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Accuracy of fine needle aspiration biopsy to diagnose lymphadenopathy in Dr.Sardjito General Hospital, Yogyakarta, Indonesia

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ABSTRACT

Lymphadenopathy is a non-specific enlargement of lymph nodes which may be caused by infection, cancer, or autoimmune disease. To date, only a few studies reported the diagnostic value of fine-needle aspiration biopsy (FNAB) in lymphadenopathy. This study was performed to evaluate diagnostic reliability of FNAB for benign and malignant lymphadenopathy. This was a retrospective cross-sectional study. The obtained data were statistically analyzed for its sensitivity, specificity, and accuracy. Out of 126 collected FNAB cases with histopathological confirmed results in Dr. Sardjito General Hospital, Yogyakarta, 85 (67.4%) were malignant lymphadenopathy, consisting of 42 metastatic tumor cases, 38 non-Hodgkin lymphoma (NHL) cases, and 4 Hodgkin lymphoma (HL) cases.The overall diagnostic sensitivity, specificity, and accuracy of FNAB in lymphadenopathy was 85.88, 70.73, and 80.95%, respectively. In diagnosing metastatic tumors, FNAB had sensitivity of 83.33%; specificity of 89.28%; and accuracy of 87.3%. The sensitivity, specificity, and accuracy of FNAB in diagnosing NHL was 60.52, 94.31, and 84.12%, respectively. FNAB had a sensitivity of 25%, specificity of 95,90%, and accuracy of 93.65% to diagnose HL. Meanwhile, the accuracy of FNAB in diagnosing malignancies in generalized lymphadenopathy, head-neck lymphadenopathy, and inguinal lymphadenopathy was 90.90; 81.39 and 44.44%, respectively. In conclusion,FNAB has moderate diagnostic value in diagnosing overall malignant lymphadenopathy, including metastatic tumors. FNAB also has some limitations in diagnosing NHL and HL, with sensitivity less than 70% for both diseases. However, it has high accuracy to diagnose generalized lymphadenopathy.

Keywords:
FNAB;
malignant;
lymphadenopathy;
Non-Hodgkin lymphoma;
Hodgkin lymphoma;

ABSTRAK

Limfadenopati adalah pembesaran kelenjar getah bening non-spesifik yang mungkin disebabkan oleh infeksi, kanker, atau penyakit autoimun. Sampai saat ini, hanya beberapa penelitian yang melaporkan nilai diagnostik biopsi aspirasi jarum halus/*fine-needle aspiration biopsi* (FNAB) pada limfadenopati. Penelitian ini dilakukan untuk memberikan diagnostik FNAB yang teruji pada limfadenopati jinak dan ganas. Ini adalah penelitian potong lintang retrospektif. Data yang diperoleh dianalisis secara statistik untuk sensitivitas, spesifisitas, dan akurasinya. Dari 126 kasus FNAB yang dikumpulkan dengan hasil histopatologis dikonfirmasi di Rumah Sakit Umum Pusat Dr. Sardjito Yogyakarta, 85 (67,4%) adalah limfadenopati ganas, yang terdiri dari 42 kasus tumor metastasis, 38 kasus non-Hodgkin lymphoma (NHL), dan 4 kasus Hodgkin lymphoma (HL). Sensitivitas diagnostik keseluruhan, spesifisitas, dan akurasi FNAB dalam limfadenopati berturut-turut adalah 85,88; 70,73 dan 80,95%. Dalam mendiagnosis tumor metastasis, FNAB memiliki sensitivitas 83,33%; spesifisitas 89,28%; dan akurasi 87,3%. Sensitivitas, spesifisitas, dan akurasi FNAB dalam mendiagnosis NHL berturut-turut adalah 60,52; 94,31 dan 84,12%. FNAB memiliki sensitivitas 25%; spesifisitas 95,90%; dan akurasi 93,65% untuk mendiagnosis HL. Sementara itu, akurasi FNAB dalam mendiagnosis keganasan pada limfadenopati umum, limfadenopati kepala-leher, dan limfadenopati inguinal masing-masing adalah 90,90; 81,39 dan 44,44%, masing-masing. Dapat disimpulkan, FNAB memiliki nilai diagnostik sedang dalam mendiagnosis limfadenopati ganas secara keseluruhan, termasuk tumor metastasis. FNAB juga memiliki beberapa keterbatasan dalam mendiagnosis NHL dan HL, dengan sensitivitas kurang dari 70% untuk kedua penyakit. Namun, ia memiliki akurasi tinggi untuk mendiagnosis limfadenopati generalisata.

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INTRODUCTION

Lymphadenopathy is defined as enlargement of lymph nodes, either caused by infiltration of inflammatory cells or invasion of neoplastic cells into lymph nodes. Lymphadenopathy lasting less than two weeks or more than one year without progressive increase in size shows a very low possibility of being neoplastic.[1] Lymph nodes serve as an important part of the defense system of the human body that become secondarily involved in infectious diseases, neoplastic disorders, lipid storage diseases, endocrine disorders and in many other conditions such as sarcoidosis and histiocytosis.[2] The prevalence of malignancy is considered to be quite low among all patients with lymphadenopathy.[1]

Tissue biopsy is the gold standard method to establish the etiology of lymphadenopathy, however fine needle aspiration biopsy (FNAB) has been reported as an approach to make initial diagnosis since it is less invasive, simpler, and cheaper. The FNAB method is applied by merely using a needle without the need of general anesthesia or complicated surgical procedures. It is considered as the easiest and fastest diagnostic modality to establish the diagnosis.[3] Some studies reported that FNAB showed high accuracy in diagnosing neoplasia in many organs, such as thyroid, breast, soft tissue, bone, and lymph nodes.[4-8] Sengupta reported that FNAB showed 90% sensitivity, 100% specificity, and 98.88% accuracy in establishing diagnosis in thyroid nodules. Meta-analysis study of FNAB accuracy in breast cancer showed that the sensitivity and specificity were high, with 92.7 and 94.8%, respectively.[5] FNAB sensitivity and specificity in inguinal lymph nodes were reported to be 91.7 and 98.2%, respectively.[8] However, the role of FNAB for initial diagnosis and sub-classification of primary lymphoid malignancy is still controversial. Cytological diagnosis in FNAB is almost always needed to be followed with tissue biopsy.[9] FNAB is also reported useful to detect non-neoplastic lesions such as dermatopathic lymphadenopathy and other lymphadenopathy caused by HIV or tuberculosis.[10-12] Diagnostic value of FNAB varied in many studies, affected by material adequacy criteria, inferior sampling techniques, errors in cytologic interpretation, and limitations of the procedure.[13]

This study was performed to evaluate diagnostic value of FNAB for benign and malignant lymphadenopathy in Dr. Sardjito General Hospital, Yogyakarta, Indonesia. This research will aid hospitals to evaluate pathologists' performance in order to improve patient care.

MATERIALS AND METHODS

Subjects

This research was a retrospective cross-sectional study. Samples which fulfilled inclusion and exclusion criteria were collected from the Department of Anatomical Pathology, Dr. Sardjito General Hospital/Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, from January 2012 to December 2017 without randomization (consecutive sampling). Patients recruited for this study were patients with lymph node enlargement who underwent both FNAB and excision biopsy procedures so that the cytological findings could be confirmed with histopathological results as the gold standard of diagnosis. This study was approved by The Medical and Health Research Ethics Committee of Dr. Sardjito General Hospital/Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta.

Protocol

All FNAB were blindly performed, without any imaging guide. Immunohistochemical and other molecular examination, such as clonality test, were not available for most of cases, so that they were not used as gold standard in this study. Patients with incomplete data were excluded from the study. The dependent variable was histopathological result of excision biopsy, and the independent variable was the cytopathological finding of FNAB.

Statistical analysis

Data were presented as mean ± standard deviation (SD) or frequency or percentage and statistically analysis using SPSS and a 2x2 table to analyze the sensitivity, specificity, and accuracy.

RESULTS

Based on patients' medical records from January 2012 to December 2017, there were 1702 patients with lymphadenopathy who underwent the FNAB procedure, with 165 patients in 2012, 253 patients in 2013, 391 patients in 2014, 190 patients in 2015, 455 patients in 2016, and 248 patients in 2017. There were only 126 patients who were confirmed by undergoingexcision biopsy, 17 patients in 2012, 19 patients in 2013, 30 patients in 2014, 15 patients in 2015, 32 patients in 2016, and 13 patients in 2017. TABLE 1 demonstrated subject characteristics based on sex, age and predilection organs. Sixty-five subjects were male (51.5%) and the rest of the 61 subjects were female (48.5%). The average age in this study was 47.32±18.02 years old, and the youngest patient was 3 months old while the oldest patient was 78-year-old. The highest incidence occurred at the40-59 year-old group (47.6%). The most common site of lymphadenopathy was head-neck in 85 patients (67.5%), followed by axilla (11.9%), generalized (8.7%), inguinal (7.1%), supraclavicular (4.0%) and abdominal (0.8%).

TABLE 1. Subject characteristics based on sex, age group and predilection, year 2012-2017

Characteristics	Frequency	%
Sex		
• Male	65	51.5
• Female	61	48.5
Age		
• 0- ≤19	12	9.5
• 20-≤39	21	16.6
• 40 -≤59	60	47.6
• 60-≤69	33	26.1
Predilection		
• Head neck	85	67.5
• Abdominal	1	0.8
• Axilla	15	11.9
• Supraclavicular	5	4.0
• Inguinal	9	7.1
• Generalized	11	8.7

FNAB findings were confirmed with histopathological results as shown in TABLE 2. Analysis of 126 cases showed that FNAB findings of 85 cases (67.4%) were malignant, and 41 cases (32.6%) were benign. Histopathological resultsalso revealed that 85 cases (67.4%) were malignant and 41 cases (32.6%) were benign.

TABLE 2. FNAB results compared to histopathological results

		Histopathology		Total
		Malignant	Benign	
FNAB results	Malignant	73	12	85
	Benign	12	29	41

The calculation of diagnostic value was performed based on data in TABLE 2. Sensitivity of FNAB was 85.88% with specificity of 70.73%. positive predictive value (PPV) was 85.88%, while negative predictive value (NPV) was 70.73%. FNAB accuracy for lymphadenopathy was 80.95%.

TABLE 3. FNAB findings compared to histopathological results based on predilection area

Locations			Histopathology		Total
			Malignant	Benign	
FNAB	Head and neck	Malignant	45	8	53
		Benign	8	24	32
		n	53	32	85
	Abdominal	Malignant	1	0	1
		Benign	0	0	0
		n	1	0	1
	Axilla	Malignant	12	0	12
		Benign	2	1	3
		n	14	1	15
	Supraclavicular	Malignant	4	0	4
		Benign	0	1	1
		n	4	1	5
	Inguinal	Malignant	3	3	6
		Benign	2	1	3
		n	5	4	9
	Generalized	Malignant	8	1	9
		Benign	0	2	2
		n	8	3	11

TABLE 4. The sensitivity, specificity, PPV, NPV, and accuracy of each region for FNAB compared to histopathology

Location	Sensitivity	Specificity	PPV	NPV	Accuracy
Head and Neck	84.91	75	84.91	75	81.17
Abdominal*	100	-	100	-	100
Axilla	85.71	100	100	33.33	86.67
Supraclavicular	100	100	100	100	100
Inguinal	60	25	88.89	33.33	44.44
Generalized	100	66.67	88.89	100	90.91

PPV: positive predictive value; NPV: negative predictive value; * The specificity and NPV can't be determined because the sample was only 1.

Based on predilection area, diagnostic value analysis of FNAB procedure was performed (TABLE 3 and 4). Generalized and supraclavicular lymphadenopathy FNABs have the highest sensitivity (100%), followed by axilla (85.71%) and head-neck lymphadenopathy (84.90%). The highest FNAB specificity was neck-head (75%), followed by generalization (66.67%) and inguinal lymphadenopathy (25%). The highest FNAB accuracy was in supraclavicular lymphadenopathy (100%), followed by generalized lymphadenopathy (90.90%), axilla (86.67%), head-neck (81.17%) and inguinal (44.44%) lymphadenopathy.

TABLE 5 showed cytological diagnosis (FNAB) compared with histopathological diagnosis (excision biopsy). Based on the diagnosis of Hodgkin lymphoma (HL), Non-Hodgkin lymphoma (NHL), and tumor metastasis, diagnostic value of FNAB was analyzed by comparing cytological diagnosis with histopathological result as gold standard.

TABLE 5. Cytology (FNAB) diagnosis compared to histopathology diagnosis

FNAB	Number	Histopathology diagnosis	Number
Reactive lymphoid hyperplasia	1	Reactive lymphoid hyperplasia	1
Lipoma	1	Non-specific chronic lymphadenitis	1
No Malignant Cell	5	Cavernous hemangioma	1
		Tuberculous lymphadenitis	1
		Angiomyolipoma	1
		Chronic lymphadenitis	2
Granulomatous lymphadenitis	16	Tuberculous lymphadenitis	7
		Non-specific chronic lymphadenitis	3
		Hodgkin lymphoma	2
		Non-Hodgkin lymphoma	3
		Lymphangioma	1
Suppurative lymphadenitis	7	Granulomatous lymphadenitis	2
		Tuberculous lymphadenitis	2
		Non-specific lymphadenitis	1
		Metastatic melanoma	1
		Metastatic undifferentiated carcinoma	1

Chronic lymphadenitis	12	Non-specific chronic lymphadenitis	3
		Granulomatous lymphadenitis	1
		Tuberculous lymphadenitis	1
		Benign hemangiopericytoma	1
		Non-Hodgkin lymphoma	4
		Metastatic undifferentiated carcinoma	1
		Metastatic ductal carcinoma	1
Lymphoma, undetermined type	6	Non-Hodgkin lymphoma	3
		Chronic lymphadenitis	2
		Tuberculous Lymphadenitis	1
Hodgkin lymphoma	6	Hodgkin lymphoma	1
		Non-Hodgkin lymphoma	3
		Chronic lymphadenitis	1
		Metastatic undifferentiated carcinoma	1
Non-Hodgkin lymphoma	28	Non-Hodgkin lymphoma	23
		Chronic lymphadenitis	1
		Granulomatous lymphadenitis	2
		Metastatic carcinoma	2
Metastatic undifferentiated carcinoma	11	Metastatic undifferentiated carcinoma	5
		Hodgkin lymphoma	1
		Non-Hodgkin lymphoma	2
		Non-specific chronic lymphadenitis	2
		Metastatic adenocarcinoma	1
Metastatic squamous cell carcinoma	4	Metastatic squamous cell carcinoma	4
Metastatic ductal carcinoma	11	Metastatic ductal carcinoma	10
		Metastatic invasive mixed ductal-lobular carcinoma	1
Metastatic lobular carcinoma	4	Metastatic lobular carcinoma	3
		Metastatic ductal carcinoma	1
Metastatic adenocarcinoma	7	Metastatic adenocarcinoma	3
		Metastatic squamous cell carcinoma	1
		Metastatic papillary carcinoma	2
		Metastatic undifferentiated carcinoma	1
Metastatic melanoma malignancy	3	Metastatic melanoma	2
		Non-specific chronic lymphadenitis	1
Metastatic follicular carcinoma	1	Metastatic ductal carcinoma	1
Metastatic small cell tumor	1	Metastatic small cell tumor	1
Malignant, undetermined type	2	Non-specific chronic lymphadenitis	1
		Sinus histiocytosis	1
Total	126	Total	126

Malignant cases revealed in this study were lymphoma, either HL and NHL subtype, and various types of metastatic cases that were summarized in TABLE 6 to 8. In diagnosing HL, FNAB showed very low sensitivity (25%), but high in specificity (95.90%) and accuracy (93.65%) (TABLE 5). In diagnosing NHL, FNAB showed low sensitivity (60.52%), but high in specificity (94.31%) and accuracy (84.12%) (TABLE 6). Interestingly, as demonstrated in TABLE 7, FNAB showed high sensitivity (83.33%), specificity (89.28%) and accuracy (87.3%) to diagnose tumor metastasis in lymph node. Terminology of undetermined type of lymphoma in this study is used as a cytological term due to inability to differentiate lymphoma into its subtypes.

TABLE 6. FNAB results in diagnosing hodgkin lymphoma

		Histopathology		Total
		(+)	(-)	
FNAB	(+)	1	5	6
	(-)	3	117	120
Total		4	122	126

TABLE 7. FNAB results in diagnosing non-hodgkin lymphoma

		Histopathology		Total
		(+)	(-)	
FNAB	(+)	23	5	28
	(-)	15	83	98
Total		38	88	126

TABLE 8. FNAB results in diagnosing tumor metastasis in lymph node

		Histopathology		Total
		(+)	(-)	
FNAB	(+)	35	9	44
	(-)	7	75	82
Total		42	84	126

DISCUSSION

Despite the high number of FNAB lymphadenopathy cases, there were limited samples eligible to be included in this study since not all subjects, particularly benign cases, underwent excision biopsy for diagnosis confirmation. Few cases with excision biopsy were performed in other hospital (s), thus histopathological data was difficult to obtain. Therefore, only 126 subjects were included in this study.

In this study, lymphadenopathy occurred almost evenly between females and males with ratio 1:1.06. This result is comparable with previous reports showing that males are more prone to have lymphadenopathy compared to females, with ratio of 1.5:1.[14] Some

factors have been reported as the cause of gender disparity in malignancy, including sex hormones, genetic materials, environmental exposure, and epigenetic factors. Higher malignancy incidence in males was related to environmental and occupational exposure such as diet, smoking, and sun exposure.[15] Immunological response in cancer is different in males and females due to x-linked gene expression and steroid hormones. Estrogen functions as immunomodulator by stimulating immune cells and decreasing cytokine production such as IL-6. High estrogen levels in females decrease susceptibility of infection. Thus, males have higher susceptibility for acquiring infections compared to females. This pattern may cause different disease incidences in males and females.[15]

Lymphadenopathy mostly occurred in the age groups 40-59 year old (47.6%), 60-79 year old (26.1%), and 20-39 year old (16.6%)in this study. In a previous study, the highest case occurred at the 6th decade (18%) of age, followed by the 4th decade (16.8%) and 5th decade (15.9%).[14] Another study with 1022 patients showed a different pattern with the majority of the patients in the range of 21-50 years old.[16]

The most common site of lymphadenopathy was head-neck in 85 patients (67.5%), followed by axilla, generalized site, inguinal, supraclavicular, and abdominal regions. This study found similar results with previous studies, reporting that most of lymphadenopathy occurred localized, especially in the head-neck or cervical region.[16-20]

Sensitivity, specificity, and accuracy of lymphadenopathy FNAB in this study were moderate; 85.88%, 70.73%, and 80.95% respectively. Previous study in 233 research subjects, reported high sensitivity (94%), and specificity (99%) of lymphadenopathy FNAB.[21] A study by Haquewith 81 cases showed that sensitivity and specificity of FNAB in lymph node were 82.76 and 97.92%, respectively.[22]

Based on location, FNAB sensitivity was the highest in generalized and supraclavicular lymphadenopathy, specificity was highest in head and neck lymphadenopathy, and the highest accuracy to detect malignancy was in generalized and supraclavicular lymphadenopathy. Location of lymph node enlargement may affect the diagnostic value of FNAB. Generalized lymphadenopathy has higher sensitivity and specificity since it is predictable that generalized lymphadenopathy is caused by serious infection, autoimmune disorders, and malignancy for example, lymphoma, leukemia, or metastasis. Head and neck lymph nodes are also a predictable common region of metastatic tumors of nasopharyngeal cancer.[23] Previous study conducted in 94 patients with head and neck lymphadenopathy reported that sensitivity, specificity, and accuracy of the study was 94.7, 89.3, and 92.9%, respectively.[24] In contrast to previous report, a study of inguinal lymphadenopathy in 210 patients showed high sensitivity (91.7%) and specificity (98.2%).[7] The low results of sensitivity, specificity, and accuracy of FNAB in inguinal lymphadenopathy in this study weremostly caused by the small sample size (11 cases).

FNAB sensitivity to diagnose HL in this study is very low (25%). However, the specificity and accuracy were high, 95.90 and 93.65%, respectively. Prasad *et al.*[25] conducted a similar study on 1041 subjects and the results showed that the sensitivity was 30% and the specificity was 98.6%. Limitation of FNAB in diagnosing HL was also reported by another study, where only 45% of subjects were diagnosed with HL based on histopathological results.[26]

In this study, there were 3 false negative cases diagnosed as metastatic undifferentiated carcinoma (1 case)

and granulomatous lymphadenitis (2 cases). Three false positive cases were diagnosed as NHL in cytology examination, while the other two were diagnosed as chronic lymphadenitis and metastatic undifferentiated carcinoma. Granulomatous response, fibrosis and co-infection have been reported as confounding factors in diagnosing HL using FNAB.[27]

FNAB sensitivity to diagnose NHL was higher than HL (60.52%). Meanwhile, the specificity and accuracy were quite high, with 94.31 and 84.12%. Previous studyreported that sensitivity and specificity FNAB in NHL were higher, with 80.3 and 58.33%, respectively.[25] Another study reported that FNAB sensitivity was variable, from 0 to 100%, with average of 74%.[28]

In this study, there were 15 false negative cases, diagnosed as chronic lymphadenitis, granulomatous lymphadenitis, and metastatic undifferentiated carcinoma. Five false positive cases were chronic lymphadenitis, granulomatous lymphadenitis, and metastatic carcinoma identified as NHL. Cytology sample scontaining abundant histiocytes will be difficult to be distinguishedfrom granulomatous lesions since FNAB does not show tumor structure.[13] Sensitivity and specificity of FNAB can be affected by many factors, for example, sample adequacy, superinfection accompanied by necrotic appearance, fibrosis, clinical and radiology information, pathologist experience in interpreting cytology specimen and special methods of staining.[29]

FNAB sensitivity, specificity, and accuracy for metastatic tumors were high, with 83.33, 89.28, and 87.3%, respectively. These results corresponded with previous studies, showing values consistently above 90%.[25,30] In this study, there were 7 false negative cases, where metastatic carcinoma was diagnosed as chronic lymphadenitis, suppurative lymphadenitis, HL, and NHL. There were 9 false positive cases, identified as chronic lymphadenitis, NHL, and HL in histopathology examination. False negative results may occur in inadequate or unsatisfactory sampling due to difficult lymph node location, for example, deep inguinal lymph nodes.[31] In such cases, ancillary tools may be used to achieve better visualization. Anotherreporthas mentioned similar false positive cases such as in our study, HL, and reactive lymphoid hyperplasia, with the main reason of error was lack of information on clinical examination.[24] Insufficient sampling has been reported as another cause of false positive cases, along with the enlargement of reactive lymph node.[32] False positive FNAB results may contribute to adverse consequences, depending to which diagnosis chosen. Fluoroscopy, ultra-sonography (USG), or computerized tomography (CT) scan can be used to directly guide pathologists or radiologists to obtain samples from the proper location of the tumor.[33] Some studies reported that imaging such as USG can increase accuracy of FNAB.[18] In cases where pathologists found difficulty to distinguish malignant from benign lesions, immunostaining for lymphoma or metastatic tumors was helpful to establish the diagnosis.[30]

Diagnostic value variations of FNAB techniqueexisted in many previous studies. These are caused by several factors, including whether the collected material is sufficient during sampling or inferior sampling techniques. Some errors in cytologic interpretation can contribute to the variation of diagnostic value as well. Furthermore the complicated location of FNAB may also cause the limitations of the procedure so that imaging guided such as USG is needed.[13]

CONCLUSION

In this study, FNAB as a diagnostic

modality showed low to moderate value in diagnosing overall malignancy in lymphadenopathy cases, including metastatic tumors. It had several disadvantages in diagnosing NHL and HL with sensitivity less than 70%. Some factors, such as sample adequacy, superinfection, fibrosis, clinical and radiology information, pathologist experience in interpreting cytological specimens, and staining methods may affect the diagnostic value of FNAB. Although this study only used data from FNAB without imaging guide, ancillary modalities (USG or CT-scan) may be used to improve sample adequacy. Complete clinical and imaging information along with experiences in accurate cytological interpretation are crucial to support pathologists in establishing a reliable diagnosis.

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