

Biopsy of cervical lymph node

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Abstract

Objective: This report examines 60 non-cancer patients who underwent a cervical lymph node biopsy, and discusses the value of the cervical lymph node biopsy as a diagnostic tool.

Methods: Sixty patients with cervical lymph node enlargement who had lymph node biopsies at the Juntendo University between 2004 and 2007 were examined. The clinical parameters including age, size of the lymph node, white blood cell (WBC), C reactive protein (CRP), lactate dehydrogenase (LDH), soluble interleukin-2 receptor (sIL-2r) were measured at initial examination. Fine needle aspiration cytology was carried out in all patients. The patients were divided into 2 groups, including the malignant lymphoma (ML) group and the benign disease group. These groups were compared based on the patient's clinical parameters.

Results: Serum levels of LDH, sIL-2r, age and lymph node size in the ML group were significantly higher than in the benign group. WBC and CRP showed no significant differences. Simple regression analysis showed that there are correlation between the size of enlargement lymph node and serum levels of LDH and sIL-2r in ML group.

Conclusion: The results of this study suggest that a biopsy should be considered early to patients with an advanced age, large swollen lymph nodes or high levels of serum sIL-2r or LDH.

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1. Introduction

Lymphadenopathy is a symptom which frequently presents in primary care settings and affects patients of all ages [1]. Although the observation of lymph node enlargement sometimes raises fears about serious illness, it usually results from benign infectious causes. The fear arises due to the spectra of causes which include microbial, hematological, neoplastic, and connective tissue disorders [2]. Several studies on peripheral lymphadenopathy in various countries have shown that cervical lymph nodes are the most frequently enlarged and biopsied of all peripheral lymph nodes [3–5]. A non-invasive diagnostic evaluation may uncover the cause of lymphadenopathy, but in numerous cases a definite diagnosis

cannot be established. In such cases the doctor should decide either to wait and closely observe the patient or to proceed to a lymph node biopsy. It is obvious that a delayed diagnosis of a serious, especially malignant, disease may be critical for the patient. On the other hands an unnecessary lymph node biopsy may increase patients' anxiety and the medical costs [6]. However, the decision-making process for a lymph node biopsy has been empirical. Identifying patients with peripheral lymphadenopathy who will benefit from lymph node biopsy is often difficult. Many investigators have tried to identify the clinical variables that are associated with malignant or granulomatous peripheral lymphadenopathy. When otorhinolaryngologists are faced with these patients, the critical task is to differentiate benign from malignant lymph nodes.

Making a diagnosis of metastatic cancer is not difficult even in primary unknown carcinoma. Fine needle aspiration cytology (FNAC) is highly reliable in the identification of

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metastatic carcinoma, thus limiting the requirement for a diagnostic excision biopsy in many patients. On the other hand, many cases of other diseases with lymph node swelling cannot be diagnosed without a lymph node biopsy. Similarly in this hospital, many cervical lymph node biopsies were required for the definite diagnosis.

This report examines 60 non-cancer patients who underwent a cervical lymph node biopsy, and discusses the value of the cervical lymph node biopsy as a diagnostic tool.

2. Patients and methods

Sixty patients with cervical lymph node enlargement who had lymph node biopsies at the Juntendo University between 2004 and 2007 were examined. They included 28 males and 32 females. Their ages ranged from 20 to 88 years (median: 53). No patient had received any treatment before the biopsy and patients with carcinoma were excluded. Lymph node biopsy was performed when a clinically significant enlarged lymph node persisted or increased in size despite the appropriate therapy; other diagnostic tests had failed to show its etiology, and when malignant lymphoma (ML) was suggested, there was a suspicion of serious underlying disease.

At least one histological section stained with hematoxylin and eosin was examined in each case. The diagnosis of ML is made through a pathologic examination of an adequately sampled, handled, and fixed tissue specimen. Where possible, care should be taken to provide intact samples large enough to provide meaningful nodal architecture information on which to base pathologic diagnosis. All permanent specimens should be submitted dry or in saline to allow immunohistochemical and flow cytometric studies to complement traditional pathology.

The clinical parameters including age, size of the lymph node, white blood cell (WBC), C reactive protein (CRP), lactate dehydrase (LDH), soluble interleukin-2 receptor (sIL-2r) were measured at initial examination. The largest lymph node was measured by ultrasound in a patient who had multiple swollen lymph nodes. FNAC were carried out in all patients. Aspirations were performed using a 23-gauge needle, and a 20-ml syringe under ultrasound guidance. All specimens were adequate for cytological examination. Paired slides were prepared, with 1 slide air dried and stained with Wright–Giemsa solution, and the other alcohol-fixed for Papanicolaou staining. No flow cytometry, immunohistochemistry or evaluation of the surface marker were performed. The final diagnosis indicated that more than half the patients had malignant lymphoma (39; 65%), 5 had tuberculosis, 3 had sub-acute necrotizing lymphadenitis, and 13 had non-specific lymphadenopathies.

The patients were divided into 2 groups, including the ML group and the benign disease group, including those with tuberculosis, sub-acute necrotizing lymphadenitis and reactive lymphadenopathy, to compare based on the

patient's clinical parameters. Eleven patients who were made diagnosis of ML by FNAC were excluded in ML group. Student's unpaired *t*-test was used to compare the clinical parameters. Simple regression analysis assessed the linear relationship between each clinical parameters in ML group. *P*-Values less than 0.05 were considered to be significant.

3. Result

Some clinical parameters are shown in Table 1. These parameters were compared between the ML and benign lymphadenopathy group. Serum LDH, sIL-2r, age and lymph node size in the ML group were significantly higher than in the benign group. WBC and CRP showed no significant differences. All patients with benign lymph node enlargement had no malignant findings with FNAC. No false positive cases were observed. Eleven out of the 39 patients with ML had FNAC reported as ML. Each of clinical parameters was compared by a single regression analysis. The correlation between preoperative variables is shown in Table 2. There were significant correlations between level of sIL-2r and, CRP ($r = 0.900$, $P < 0.001$) or LDH ($r = 0.896$, $P < 0.001$). Level of LDH is correlated with CRP significantly ($r = 0.822$, $P < 0.001$). The other

Table 1
Clinical parameters of ML are compared with benign disease

	Benign	ML	<i>P</i> -Value
Age (years)	44.3	57.7	<0.01
WBC ($\times 10^9/l$)	5.84	5.92	NS
CRP (g/dl)	0.42	1.73	NS
LDH (IU/l)	174.4	242.6	<0.05
Size (mm)	19.4	26.9	<0.05
sIL-2r (U/ml)	815.4	2523	<0.05

Age, LDH, size of the lymph node and sIL-2r in ML patients were significantly higher than benign disease.

Table 2
Simple regression analysis assessing the linear relationship between each clinical parameters in ML group

	Age	WBC	CRP	LDH	sIL-2r
Age	–				
WBC	–0.052 NS	–			
CRP	–0.228 NS	0.083 NS	–		
LDH	0.048 NS	–0.084 NS	0.832 $P < 0.001$	–	
sIL-2r	–0.061 NS	–0.052 NS	0.901 $P < 0.001$	0.900 $P < 0.001$	–
Size	0.227 NS	–0.162 NS	–0.179 NS	–0.040 NS	–0.054 NS

The correlation between preoperative variables is shown.

parameters were not correlated with each other. The patients were divided into the following two groups: one had 28 patients with normal values of IL-2 or LDH, while the other had 11 patients with higher values of these parameters. Proportions of ML in each group were 47.4% and 90.9%, respectively. The difference of these proportions is statistically significant.

4. Discussion

An enlargement of the peripheral lymph nodes is a common clinical presentation of a variety of pathological conditions, including lymphoreticular malignancies, metastatic malignant processes, reaction to local or systemic inflammatory conditions, and in response to systemic autoimmune diseases and immunization. Most cases of lymphadenopathy in all generations are due to infection or benign diseases. The clinical history, physical examination, and laboratory and radiological investigations may give important clues for the diagnosis. However, some cases require an excisional biopsy for the definite diagnosis. In the general population, only 3.2% of cases required biopsy and only 1.1% had malignancy [7]. Greenfield and Jordan presented an algorithm for the clinical investigation of lymphadenopathy in a primary care practice. After the exclusion of local lesions or infections, toxoplasmosis, cytomegalovirus, and Epstein-Barr virus mononucleosis, they suggested that other systemic conditions must be pursued by biopsy of the persistent enlarged lymph nodes [8]. However, other authors, predominantly head and neck surgeons, have previously warned against untimely lymph node biopsies [9], particularly in elderly patients, who might have an occult primary tumor in the head and neck area or who had a cursory examination without discovering the primary site [10]. However, the identification of patients with peripheral lymphadenopathy who will benefit from a lymph node biopsy is often difficult. Many investigators have tried to identify clinical variables that are associated with malignant peripheral lymphadenopathy.

In this study, only 11 of 39 patients with the diagnosis as ML showed a true positive finding on preoperative FNAC. This value is inadequate to determine whether or not a lymph node biopsy should be performed. FNAC is often the first line of investigation (screening test) used in cases of lymphadenopathy to differentiate between lymphoreticular malignancy, metastatic cancer, specific infections such as tuberculous lymphadenitis, and non-specific reactive lymphadenitis [11,12]. However, the distinction between reactive and malignant lymphoid proliferations is the most difficult aspect in lymph node FNAC. This is not surprising, given that excised lymph nodes commonly cause diagnostic difficulties despite the advantage of architectural preservation in biopsy specimens. Aspirate specimens from cases of high grade lymphoma and Hodgkin's disease may show an obvious cytomorphological abnormality, but the diagnosis of low

grade lymphomas in cytological preparations is most often based on the presence of a relatively monomorphic lymphoid population, thus contrasting with the typically polymorphous cell pattern seen in reactive proliferations [13,14]. McNeely reviewed 14 histologically confirmed follicular lymphomas in which FNAC had been performed before the biopsy; four cases had been misinterpreted as reactive lymphoid hyperplasia. Ten of 16 follicular lymphomas were misdiagnosed on aspiration cytology in the study by Pilotti et al. [15,16]. Therefore, it is important that pathologists and clinicians are aware that negative FNAC results do not exclude lymphoma in patients with unexplained lymph node enlargement, and that lymph node biopsy should be considered depending on the clinical findings, especially in a facility in which flow cytometry cannot be administered. The indications for performing a lymph node biopsy in patients with ML include not only FNAC but also other clinical parameters [17].

In this study, serum LDH, sIL-2r, size of lymph node and age of the patients with ML were higher than benign lymph node enlargement. These findings indicated that the risk of ML in cervical enlarged lymph node increases with the age, size of the lymph node, serum LDH levels and sIL-2r. Simple regression analysis showed that there are correlation between the size of enlargement lymph node and serum levels of LDH and sIL-2r. On the other hand, the size of enlargement lymph node correlated with serum levels of LDH or sIL-2r. Moreover, patients with increased values of serum sIL-2r and LDH had a higher rate of ML than the others, and this difference was statistically significant. Hence, a patient with high levels of serum LDH or sIL-2r has high possibility of ML, even though the patient has small lymph node. Measurement of these parameters is not invasive. Screening for the biopsy may be necessary. However, whether these examinations should be undergone in all patients with lymphadenopathy remains controversial.

There have been no previous reports indicating an association between a biopsy of head and neck lymphadenopathy and the serum sIL-2r level. The interleukin-2 receptor system plays important roles in the activation and proliferation of lymphocytes. IL-2r is expressed on the cell membrane of lymphocytes [18] not only on the surface of activated T or B lymphocytes, but also on tissues in lymphoid malignancies. sIL-2r is released from the cell membrane by cleavage of IL-2r [19]. Measurement of sIL-2r level may represent a useful tool in monitoring disease status and the effect of therapy in several hematological malignancies such as adult T-cell leukemia, chronic lymphocytic leukemia, hairy cell leukemia, Hodgkin's disease, non-Hodgkin's lymphoma and also in patients with solid malignancies such as lung cancer [20–25]. Recently, an elevation of serum sIL-2r levels has been reported in patients with carcinoma of the digestive organs, such as gastric carcinoma, pancreatic adenocarcinoma, colon cancer and esophageal carcinoma. However, the clinical significance of serum sIL-2r levels is not well known. The present study is consistent with the findings of the previous study.

First, metastatic cancer is distinguished from other diseases associated with cervical lymph node enlargement. If a definitive diagnosis cannot be made by FNAC or other examinations, the patient must be followed closely, with a working diagnosis of non-specific lymphadenopathy. Regular follow-up is absolutely necessary for such patients with lymphadenopathy which is not definitely indicated for a lymph node biopsy. However, the results of this study suggest that a biopsy should be considered in patients with an advanced age, large swollen lymph nodes or high levels of serum sIL-2r or LDH without additional and reiterative clinical examination.

5. Conclusion

In conclusion, when a definitive diagnosis cannot be made by FNAC or other examinations, a biopsy is administered to patients with an advanced age, large swollen lymph nodes or high level of sIL-2r or LDH should be considered.

The above-described predictive criteria may contribute significantly to the decision to perform a lymph node biopsy, while also assist in the clinical judgment, especially for inexperienced physicians. The use of such criteria could also potentially reduce the extent of laboratory investigations during the evaluation of patients with lymphadenopathy, thereby reducing the overall health care costs.

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