Predictors of the necessity for lymph node biopsy of cervical lymphadenopathy

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ABSTRACT

Purpose: Enlargement of cervical lymph nodes is required for early and accurate diagnosis of malignant lymphoma (ML). Lymph node biopsy is still indispensable for accurate diagnosis of lymph node enlargement in the lateral neck.
Material and methods: We retrospectively investigated the characteristics of lymph nodes on both ultrasonography (US) and computed tomography (CT), and blood biomarkers including serum thymidine kinase (TK) and soluble interleukin-2 receptor (sIL-2R) in 19 patients who underwent cervical lymph node biopsy.
Results: Pathological diagnosis was ML in 8 patients, reactive lymphadenopathy (RL) in 8, and purulent lymphadenitis (PL) in 3. TK levels were significantly higher in patients with ML than in patients with RL, demonstrating positive correlations with sIL-2R and lymph node size on CT image. The shape of lymph nodes on US in all of the 8 patients diagnosed with RL was flat, whereas the shape in 7 of 8 patients diagnosed with ML was round. Lymph node size $\geq$19.5 mm at an axial section on CT image was used as a cut-off value to differentiate ML from other pathologies, offering 90.9% sensitivity and 87.5% specificity.
Conclusion: Sonographic and CT evaluation combined with high TK level might be useful in determining the need for early biopsy.

1. Introduction

We have faced difficulties in diagnosing patients presenting with enlarged cervical lymph nodes, because this is one of the clinical presentations of malignant lymphoma (ML), which requires early and accurate diagnosis. Imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), and positron emission tomography (PET)-CT are helpful to speculate the size, site, contents, and malignancy of lesions in the neck. It is usually not difficult to diagnose the cervical metastatic carcinoma using US and fine needle aspiration cytology (FNAC).

Many reports have noted that serum biomarkers such as thymidine kinase (TK) and soluble interleukin-2 receptor (sIL-2R) reflect the tumor burden or cell proliferation rate in patients with Hodgkin lymphoma (HL) (Eriksson et al., 1985; Gause et al., 1992), non-HL (NHL) (Rehn et al., 1995; Motokura et al., 1995), or adult T-cell leukemia lymphoma (ATLL) (Kamihira et al., 1994; Sadamori et al., 1995), suggesting the potential utility of TK and sIL-2R as prognostic markers in place of other laboratory parameters. However, preoperative examinations are of limited use in determining the clinical diagnosis. Lymph node biopsy is therefore often performed for histological diagnosis.

Although Orita et al. (2013) suggested that sonographic evaluation combined with serum levels of lactate dehydrogenase (LDH) and sIL-2R is useful in determining the need for biopsy, few studies have described useful parameters for initial diagnosis in patients manifesting enlargement of cervical lymph nodes. To avoid

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unnecessary early biopsy, we retrospectively investigate the characteristics of lymph nodes on imaging modalities such as US and CT, and blood biomarkers including serum TK, sIL-2R, LDH, and C-reactive protein (CRP) in 19 patients who underwent cervical lymph node biopsy. We discuss the relationships between preoperative information and postoperative pathological diagnosis, and suggest useful predictors of the need for early biopsy.

2. Material and methods

2.1. Patient population and methods

A total of 19 consecutive patients (10 males and 9 females) underwent extirpation of cervical lymph nodes for histological diagnosis by Satoh K. at Saiseikai Matsusaka General Hospital between 2010 and 2014. Patients in whom metastasis from another carcinoma was already strongly suspected before biopsy were excluded from the present study. All patients were evaluated by physical examination, US, CT, and measurement of serum TK, sIL-2R, LDH, and CRP levels at initial examination, followed by cervical lymph node biopsy. According to the pathological diagnosis, we retrospectively divided the 19 patients into three groups: reactive lymphadenopathy (RL), purulent lymphadenitis (PL), and ML.

Relationships between the pathological diagnosis and the following parameters were examined, as follows: age; lymph node size, or maximal diameter of lymph nodes on US and CT; shape of lymph nodes on US and CT image (flat or round); serum levels of TK, sIL-2R, LDH, and CRP; and period from the initial presentation to the cervical biopsy. Lymph node characteristics on US and CT were evaluated in random order by experts specializing in interpretation of radiograms and blinded to case information.

2.2. Data analysis

All data are expressed as mean ± standard error of the mean. Values were statistically compared between the RL, PL, and ML groups using the Mann–Whitney U test. Correlations among mean diameter of lymph nodes on either US or CT, and serum biomarker levels including TK, sIL-2R, LDH, and CRP, were assessed using Spearman's rank correlation coefficient test and Pearson's product–moment correlation coefficient test. To determine the clinical accuracy of preoperative lymph node size on US and CT, and other biomarkers, the area under the receiver operating characteristic (ROC) curve (Akobeng, 2007) was compared by Z score testing. Values of $P < 0.05$ were considered to indicate statistical significance.

3. Results

An overview of the clinical characteristics including pathological diagnosis for all 19 cases is shown in Table 1. Pathological diagnosis was RL in eight patients (42%), ML in eight (42%), and PL in three (16%). According to World Health Organization criteria (Harris et al., 1997), ML was follicular lymphoma (FL) in five cases, adult T-cell lymphoma (ATL) in one case, anaplastic large-cell lymphoma (ALL) in one, and HL in one.

No significant differences in patient age, sex, and period from initial presentation to cervical biopsy were seen among the three groups. Serum LDH and CRP levels also showed no significant differences between the RL and ML groups (Table 2). In seven of the eight patients (87.5%) diagnosed with RL and two of the three patients (67%) diagnosed with PL, serum LDH and sIL-2R levels were within the normal ranges (Table 1), whereas high levels of LDH, sIL-2R, and TK were seen in two young patients with neutrophil depletion (case 7) and hyperplastic scar (case 11). TK levels were significantly higher in the ML group than in the RL group ($P < 0.05$) (Table 2). Serum levels of sIL-2R tended to be higher in the ML group than in the RL group ($P = 0.08$). Furthermore, a significant positive correlation between serum TK and sIL-2R at initial examination was noted (r = 0.64, $P < 0.01$) (Fig. 1A), whereas no correlations were evident among other markers, including LDH and CRP.

The shape of lymph nodes on US in all of the eight patients (100%) diagnosed with RL was flat, whereas the shape in seven of eight patients (87.5%) diagnosed with ML was round (Table 1). On CT image, the shape of lymph nodes in six of the eight patients (75%) diagnosed with RL was flat, the shape in seven of eight patients (87.5%) diagnosed with ML was round (Table 1). Thus the positive predictive value to characterize RL from the shape of lymph node on US image was higher than the positive value from the shape of CT image. Lymph node size at an axial section on CT image was significantly higher in the ML group than in the RL group ($P < 0.01$) (Table 2), demonstrating a significant (r = 0.61, $P < 0.05$)

Table 1
Characteristics at diagnosis of patients at initial examination.

Patient no	Age (y)	Sex	Period (days)	LDH (IU/l)	TK (U/l)	sIL-2R (U/ml)	CRP (mg/dl)	US size (mm)	US shape	CT size (mm)	CT shape	Clinical diagnosis	Histology	Group
1	57	F	54	193	5.5	296	0	13.6	1	18	1	RL	RL	RL
2	38	M	15	192	7.1	407	0.1	21	1	15	1	RL	RL	RL
3	31	F	17	NP	8.1	203	0.1	15.3	1	10	2	RL	RL	RL
4	61	M	98	165	11.2	334	0	14.8	1	10	1	RL	RL	RL
5	72	F	154	175	7.1	359	0.1	16	1	10	1	RL	RL	RL
6	34	F	31	201	18.6	237	0	15.1	1	13	2	RL	RL	RL
7	21	M	5	482	33.9	972	0.1	16	1	9	1	RL	RL	RL
8	22	M	72	197	21.1	390	1.7	16.7	1	10	1	RL	RL	RL
9	78	M	18	159	6.9	380	0.1	11	2	10	2	PL or Meta	PL	PL
10	43	F	14	188	7.6	153	0	17.4	1	12	1	RL or Inf	PL	PL
11	25	M	4	235	107.9	1874	1.6	30.8	1	40	2	PL	PL	PL
12	64	F	49	250	20.2	768	0	14.6	1	13	1	RL	FL, grade 1	ML
13	66	F	24	207	62.3	911	0	17	2	22	2	ML	FL, grade 2	ML
14	55	F	12	175	10.4	207	0	25.9	2	22	2	ML or Meta	FL, grade 2	ML
15	47	M	14	335	37.3	514	0.4	28.6	2	28	2	ML or Meta	FL, grade 2	ML
16	47	M	12	193	11.5	318	0	31	2	30	2	ML or Meta	FL, grade 2	ML
17	62	M	9	161	24.1	316	0.4	43.5	2	35	2	ML or Meta	HL	ML
18	15	M	18	200	21.6	2070	0.6	26	2	23	2	Inf	ALL	ML
19	65	F	10	173	26.4	1247	0.1	32.1	2	21	2	ML or Meta	ATL	ML

1, flat shape on US or CT; 2, round shape on US or CT; ALL, anaplastic large cell lymphoma; ATL, adult T-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin's lymphoma; Inf, infection; ML, malignant lymphoma; Meta, metastasis; NP, not performed; PL, purulent lymphadenitis; RL, reactive lymphadenopathy.