Clinical, laboratory and radiologic factors for early diagnosis of cervical lymphadenitis

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Clinical, laboratory and radiologic factors for early diagnosis of cervical lymphadenitis

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ABSTRACT

Clinical, laboratory and radiologic factors for early diagnosis of cervical lymphadenitis

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Cervical lymphadenitis is composed of various different diseases. The treatment and prognosis of each disease is multifarious. So, this study aimed to evaluate different factors among Reactive lymphadenitis (RL), Kikuchi's disease (KD) and Tuberculous lymphadenitis (TL) which are common cervical lymphadenitis.

We reviewed medical records of Gangnam Severance Hospital with cervical lymphadenitis between May 2005 and November 2014, retrospectively. And compared the clinical, laboratory and radiologic factors among three groups (n, RL=80, KD=80, TL=80).

The study included 240 Patients with the mean age 36.9. Longer duration of fever, lower level of leukocyte, lower level of Hb, lower level of platelet, lower level of albumin and higher level of AST were significant characteristics of KD than other cervical lymphadenitis. Neck mass was dominant chief complaint in RL and TL whereas it were neck swelling and fever in KD. And fever, weight

loss, fatigue and headache were common clinical features in KD. Anatomically dominant areas of lymphadenopathy were level II in RL, however it were level III, IV in KD and TL.

Comparing of radiologic features by sonography, discrete, oval shape, regular margin, homogenous lymph nodes are predominant in RL and KD rather than TL. On the contrary, presence of hypoechoic center and intranodal necrosis are distinctive features of TL. By CT images, matted nodes, presence of nodal necrosis, multiple necrosis, perinodal infiltration and calcification were remarkable features of TL.

Lastly we made a multivariate analysis among three groups, fever and leukopenia were significant predictive factors for KD comparing with RL. Leukopenia, CRP/albumin ratio and headache were significant predictive factors for RL comparing with TL. Fever, leukopenia and hypoalbuminemia were significant predictive factors for KD comparing with TL.

This knowledge about clinico-laboratoric and radiologic perspectives of cervical lymphadenitis will help to detect the disease early.

Key words : reactive lymphadenitis, kikuchi's disease, tuberculous lymphadenitis

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I. INTRODUCTION

Lymphadenopathy is the term used to describe the clinical sign of swelling of lymph nodes. Cervical area is the most common site of peripheral lymph node enlargement[1,2] and cervical lymph node enlargement is one of the frequent causes which make the patients to visit the outpatient clinic. Possible etiologies of cervical lymphadenopathy are viral or bacterial lymphadenitis, Kikuchi's disease, tuberculosis, lymphoma, toxoplasmosis, sarcoidosis, carcinoma and collagen vascular disease. Most common cause is reactive lymphadenitis (50-60%).[3,4] Malignancies presenting in the cervical region including non-Hodgkin lymphoma, Hodgkin disease, and squamous cell carcinoma of the head and neck[5] have a distinctive characteristics. Many diseases with cervical lymphadenopathy except malignancy, show similar clinical manifestations such as fever, chill, neck node swelling, tenderness and easy fatigue.[6] On the contrary,

progress and prognosis of the each diseases is multifarious.

For the examples, in reactive cervical lymphadenitis, there was no definite reported etiology[2] and mostly accompanied with nonspecific viral and bacterial infection. After a supportive care such as hydration, symptom and signs were subsided spontaneously and mostly self-limited.

Secondly, Kikuchi disease is a rare lymphohistiocytic disorder, the etiology of this disease remains unsolved. Infectious or autoimmune processes were proposed but have not been definitively confirmed[7]. Treatment guidelines have not been established, steroids, anti-inflammatory drug (NSAIDs), anti-pyretics and hydroxy chloroquine can be beneficial treatment.

In tuberculous lymphadenitis, they needs anti mycobacterial therapy for at least 6months. Two months of Rifampin, Isoniazid, Ethambutol, and Pyrazinamide followed by four months of Rifampin, Isoniazid and Ethambutol. In paradoxical reaction periods, lymph nodes become larger while on antimycobacterial treatments.[8,9]

The purpose of this study was to describe the different characteristics of confusable cervical lymphadenitis, especially among Reactive lymphadenitis (RL), Kikuchi's disease (KD) also known as histiocytic necrotizing lymphadenitis and tuberculous lymphadenitis (TL). We analyzed the clinical, laboratory and radiological differences among these three diseases and made a differential diagnosis of each disease early and correctly.

II. MATERIALS AND METHODS

1. Study subjects

We reviewed medical records of Gangnam Severance Hospital with cervical lymphadenitis between May 2005 and November 2014, retrospectively. This study includes 2,758 patients with cervical lymphadenitis, at first (Reactive lymphadenitis n=2,098, Kikuchi lymphadenitis n=445, Tuberculous lymphadenitis n=215) and then we excluded the patients who have wrong diagnosis or does not have the pathologic report.

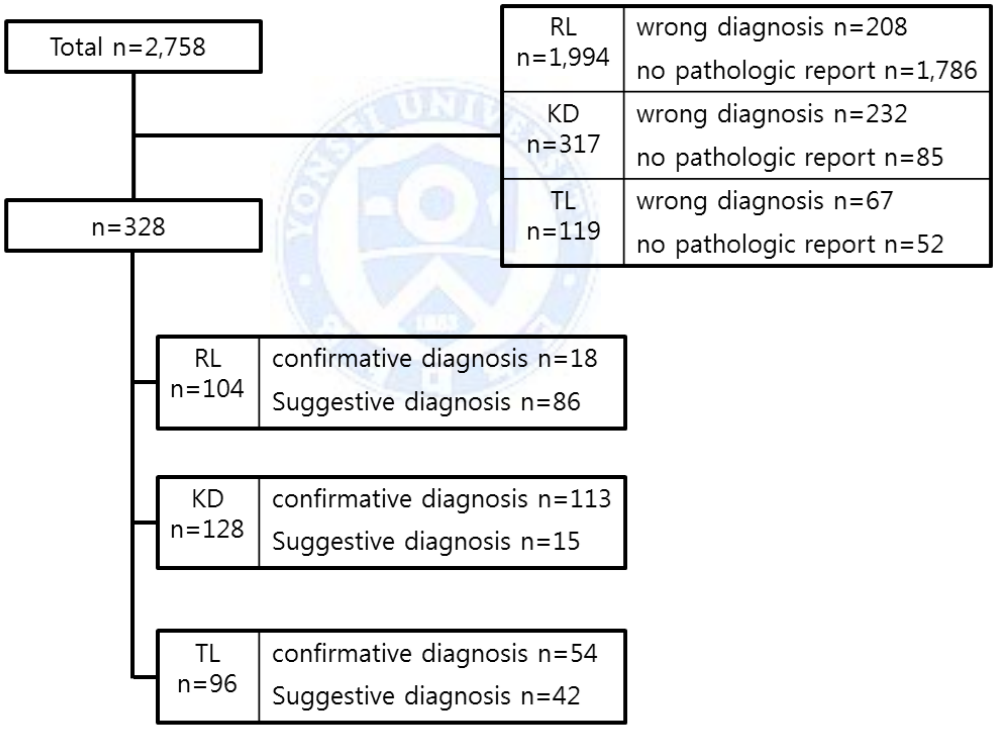

Fig 1. Study subjects

At last, there remained 328 patients (Reactive lymphadenitis n=104, Kikuchi lymphadenitis n=128, Tuberculous lymphadenitis n=96), they contained

confirmative or possible pathologic results such as favoring and suggesting lymphadenitis. And then we selected 80 patients randomly from each groups (n, RL=80, KD=80, TL=80).

2. Case definition and histopathologic diagnosis

Three diseases groups were defined by histopathologic results. All patients got one of biopsy techniques- fine needle aspiration cytology (FNAC), needle aspiration core biopsy (NAB) or excisional biopsy.

US-guided FNAC was performed to localize the lesion by radiologists with 23- to 25- gauge needle and 10ml syringe. Ultrasonographic guidance was used to confirm the correct placement of the needle in the nodule. Excisional biopsy was done by otolaryngologist and cardiovascular surgeon specialized in thoracic division with local anesthesia.

By the histologic interpretation, reactive lymphadenitis was defined as reactive hyperplasia. Kikuchi's disease was defined as specific pathologic finding- aggregates of histiocytes and lymphoid cells with abundant karryohectic debris on histology.[7] Tuberculous lymphadenitis was defined as positive reports along with acid-fast bacilli (AFB) smear, mycobacterium culture and mycobacterium PCR of lymph node material. These results contained caseating granuloma or chronic granulomatous inflammation on lymph node histology.[6,10]

3. Neck sonography and CT analysis

Neck sonographic examinations were performed with HDI 5000 (Philips Advanced Technology Laboratories, Bothell, WA, USA) with a 7-15-MHz linear array transducer or Supersonic Imagine (Aix-en-Provence, France) equipped with a 4-15-MHz linear array transducer by two radiologists with 5 to 15 years of experience in neck US.

On the basis of previous radiologic reports,[11,12] following sonographic features were reviewed for identifying three diseases groups. Node crowding (discrete

or matted), shapes (oval or round), long diameter of maximal lymph node, short diameter of maximal lymph node, margin of lymph node (regular or irregular), echogenicity (homogenous or heterogenous), presence of strong internal echo, presence of hypoechoic center, presence of peripheral halo, presence of intra nodal necrosis, number of lymph node, location of lymph node in the neck - right side, left side, both involvement, submental and submandibular level (level I), upper cervical level(level II), middle cervical (level III), lower cervical (level IV), posterior triangle (level V).

At the same time we reviewed all the neck enhanced computed tomography images. By previous reports, we selected radiologic variables.[13] Maximum size of lymph nodes, node crowding (discrete or matted), presence of lymph node necrosis, extent of necrosis (minimal means below than half of an affected nodal volume, marked means more than half of an affected nodal volume), number of necrosis (single or multiple), location of necrosis (central or peripheral), margin of necrosis (indistinct or well defined), CT attenuation of nodal necrosis (HU), presence of perinodal infiltration, presence of calcification of lymph node, presence of perinodal complication something like myositis, abscess, cutaneous fistula were reviewed by expert radiologists for making different points of three groups. We used a 64-MDCT scanner (Somatom Sensation 64 VB30, Siemens Medical Solutions, Forchheim, Germany). A total of 100 mL of contrast medium (Optiray 350; Tyco healthcare, Canada) was administered intravenously at a rate of 1.5 mL/sec using a power injector (Stellant, Medrad, Pennsylvania, USA).

4. Definition of clinical variables and laboratory findings

By clinical manifestation, we rechecked the variable symptoms and signs. Fever (>37.4℃), duration of fever (days), initial symptom (fever, neck swelling, neck mass), tenderness of lymph nodes, cough, sore throat, weight loss, night sweat, fatigue and headache.

Also, we made sure the demographic features such as Age, gender, Height (cm), Weight (kg) and Body mass index-BMI (kg/m^2). The comorbidities like hypertension, diabetes mellitus, hepatitis, malignancy, family history of tuberculosis and medication history of immune suppressant agents were included during checking of medical records.

And we evaluated laboratory findings including C-reactive protein (mg/L), procalcitonin (mcg/L), erythrocyte sedimentation rate (mm/hr), leukocyte (10^3/μL), delta neutrophil (%), hemoglobin (g/dL), red cell distribution width (%), platelet (10^3/μL), blood urea nitrogen (mg/dL), creatinine (mg/dL), albumin (g/dL), aspartate aminotransferase (IU/L), alanine aminotransferase (IU/L), antinuclear antibody (ANA), Interferon-gamma (IFN-γ) and purified protein derivative (PPD) skin test.

5. Data analysis

We compared the clinical, laboratory and radiologic characteristics among the three groups. Clinical and laboratory data were retrospectively reviewed by medical records. And two expert radiologists reviewed all of image study such as neck ultrasounds and computed tomography.

6. Statistical analysis

To evaluate the differences in clinical, laboratory and radiologic features among reactive lymphadenitis, kikuchi's disease and tuberculous lymphadenitis we used the one-way analysis of variance (ANOVA) and the χ^2 (Chi-square) tests. The one-way analysis of variance (ANOVA) was used to compare the continuous variables, the χ^2 test was used to compare the norminal variable. Statistical significance was additionally tested based on Tukey's multiple comparison test. Besides, logistic regression analysis was used to evaluate the predictive power of each significant variables. The clinical, laboratory and radiologic variables with high predictive power (P <0.05) were selected into a

binary logistic regression analysis to investigate the difference among three disease groups.

The results of this analysis were presented as odds ratio estimates with corresponding 95% confidence intervals (CIs) and *P* values from the Wald test. All statistical analyses were performed with statistical software (SPSS, version 21.0, SPSS, Chicago, IL, USA) and *P* values less than 0.05 were considered statistically significant.

III. RESULTS

1. Baseline characteristics

The study included 240 patients (55 male and 185 female subjects) with mean age 36.9. In reactive lymphadenitis mean age was 37.4±13.2, in kikuchi's disease mean age was 37.6±10.7, in tuberculous lymphadenitis mean age was 35.8±12.3 and there were no significant difference among each three groups (p=0.588). By gender, male subjects were 19 (23.8%) cases in reactive lymphadenitis, 21 (26.3%) cases in kikuchi's disease and 15 (18.8%) cases in tuberculous lymphadenitis. Family history of pulmonary tuberculosis and malignancy, especially thyroid cancer correlate with tuberculous lymphadenitis.

Table 1. Baseline characteristics among reactive lymphadenitis, kikuchi's disease and tuberculous lymphadenitis.

	Reactive Lymphadenitis (n=80)	**Kikuchi's Disease (n=80)**	**Tuberculous Lymphadenitis (n=80)**	**P-value**
Age, mean±SD (years)	37.4±13.2	37.6±10.7	35.8±12.3	0.588
Gender, male, n(%)	19(23.8)	21(26.3)	15(18.8)	0.517
Comorbidity, n(%)				
HTN	7(8.8)	3(3.8)	6(7.5)	0.419
DM	4(5.0)	0(0)	2(2.5)	0.129
Pul.Tbc	6(7.5)	6(7.5)	13(16.3)	0.112
Family history of Tbc	1(1.3)	0(0)	6(7.5)	0.010
Tonsilitis	4(5.0)	0(0)	3(3.8)	0.148
Malignancy	2(2.5)	1(1.3)	11*(13.8)	0.001
Type of biopsy, n(%)				
FNAC or NAB	68(85)	22(27.5)	31(38.8)	<0.001
Excisional biopsy	12(15)	58(72.5)	49(61.2)	<0.001

*Among eleven patients, nine had thyroid cancer

And according to type of biopsy, ultrasound guided fine needle aspiration cytology (FNAC) or needle aspiration core biopsy (NAB) was common in reactive lymphadenitis, conversely excisional biopsy was often done in kikuchi's disease and tuberculous lymphadenitis (Table1).

2. Anatomical characteristics

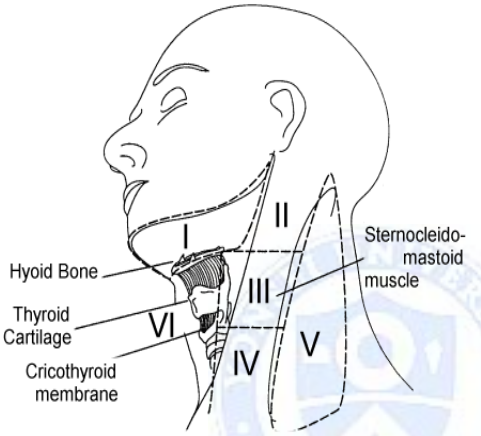

Fig 2. Anatomical location of cervical lymph nodes.

Anatomically dominant areas of lymphadenopathy were level II in reactive lymphadenitis (40(50%)), however it were level III and IV in kikuchi's disease (level III n=40(50%) and level IV n= 43(53.8%)) and tuberculous lymphadenitis (level III n=40(50%) and level IV n=52(65.0)) compared to reactive lymphadenitis. Comprehensively, frequent area of lymphadenitis was around jugular chain area rather than submental, submandibular or posterior jugular chain lesions (Figure2, Table2).

Table 2. Location of biopsied lymph nodes.

Anatomical location	RL	KD	TL	Total,n(%)
Submandibular, Submental (I)	8(10.0)	1(1.2)	4(5.0)	13(5.4)
Upper jugular (II)	40(50.0)	38(47.5)	33(41.5)	111(46.2)
Middle jugular (III)	34(42.5)	40(50.0)	40(50.0)	114(47.5)
Lower jugular, Supraclavicular (IV)	25(31.3)	43(53.8)	52(65.0)	120(50.0)
Posterior triangle (V)	29(36.3)	26(32.5)	22(27.5)	77(32.0)

3. Clinical characteristics

We compared the clinical factors among reactive lymphadenitis, kikuchi's disease and tuberculous lymphadenitis by retrograde review of medical records. Kikuchi's disease had the lowest body mass index (BMI) among three groups.

And 55 patients (68.8%) of kikuchi's disease had a fever during admission periods comparing it was only 18 patients (22.5%) in reactive lymphadenitis and 10 patients (12.5%) in tuberculous lymphadenitis. Moreover, there was the significant difference among three groups in duration of fever. It was the longest in kikuchi's disease (11.7±11.9 days) comparing that it were just 5.2±14.8 days in reactive lymphadenitis and 2.4±7.0 days in tuberculous lymphadenitis.

From a reason of admission point, neck mass was dominant chief complaint in reactive lymphadenitis and tuberculous lymphadenitis unlike it were neck swelling and fever in kikuchi's disease. Duration of initial symptom was also significantly different, it was the shortest in kikuchi's disease (21.5±19.5 days) comparing with other two diseases (73.3±147.3 in RL, 103±261.5 in TL).

Inspecting other clinical manifestations such as tenderness of lymph nodes, cough, sore throat, weight loss, night sweating, fatigue and headache closely, the weight loss ($p=0.024$), fatigue ($p=0.030$) and headache ($p<0.001$) had a signification (Table3).

Table 3. Clinical factors among reactive lymphadenitis, kikuchi's disease and tuberculous lymphadenitis.

	Reactive Lymphadenitis mean±SD or n(%)	Kikuchi's Disease mean±SD or n(%)	Tuberculous Lymphadenitis mean±SD or n(%)	P-value
BMI (kg/m^2)	22.3±3.2	20.9±3.7	22.2±3.8	0.065
Fever	18(22.5)	55(68.8)	10(12.5)	<0.001
Fever duration (days)	5.2±14.8	11.7±11.9	2.4±7.0	<0.001
T[a]	a	b	a	
Initial symptom				
Neck swelling	26(32.5)	35(43.8)	14(17.5)	<0.001
Fever	6(7.5)	29(36.3)	3(3.8)	<0.001
Neck mass	47(58.8)	16(20)	48(60)	<0.001
Duration (days)	73.3±147.3	21.5±19.5	103±261.5	0.013
T[a]	a,b	a	b	
Clinical symptoms				
LN tenderness	26(32.5)	28(35.0)	16(20.0)	0.074
Cough	5(6.3)	14(17.5)	8(10.0)	0.072
Sore throat	11(13.8)	16(20.0)	8(10.0)	0.194
Weight loss	4(5.0)	9(11.3)	1(1.3)	0.024
Night sweating	2(2.5)	6(7.5)	1(1.3)	0.089
Fatigue	13(16.3)	26(32.5)	15(18.8)	0.030
Headache	12(15.0)	28(35.0)	5(6.3)	<0.001

Statistical significance was tested by one-way analysis of variance and Chi-square among groups.

[a] The same letters indicate non-significant difference between groups based on Turkey's multiple comparison test.

4. Laboratory characteristics

In laboratorial perspective (Table4), some serologic markers had a significant difference among three disease groups. At first, leukocyte can be an important marker when we make a diagnosis of disease, initially. Leukocytopenia ($p<0.001$) was dominant in kikuchi's disease than other two diseases. Secondly, lower level of hemoglobin ($p=0.011$) and platelet ($p<0.001$) had also noticeable

means in differential diagnosis of kikuchi's disease with other two diseases. And lower level of albumin ($p<0.001$) and higher level of CRP/albumin ratio ($p=0.021$) were prominent characteristics of kikuchi's disease than other cervical lymphadenitis. Elevation of serum aspartate aminotransferase (AST) level was frequent in kikuchi's disease compared that mean serum aspartate aminotransferase (AST) level was within normal range in reactive and tuberculous lymphadenitis ($p=0.033$). All the patients were not checked the interferon-gamma level, but tuberculous lymphadenitis had predominantly positive value in interferon-gamma. It was 83.3% (10 of 12 patients) of positive value ($p=0.028$).

5. Sonographic characteristics

In comparison of sonographic characteristics, there were so many distinguishable points in tuberculous lymphadenitis than other two diseases. It means, making a diffential diagnosis of reactive and kikuchi's disease by ultrasound is very hard. Generally, long diameter and short diameter ($P<0.001$) of lymph nodes are larger in tuberculous lymphadenitis than reactive lymphadenitis and kikuchi's disease. And discreted lymph nodes were dominant in reactive lymphadenitis and kikuchi's disease comparing that there were discreted lymph nodes and matted one both in tuberculous lymphadenitis ($P<0.001$). Oval shape ($P<0.001$) and regular margin ($P<0.001$) of lymph nodes were predominant in reactive lymphadenitis and kikuchi's disease than tuberculous lymphadenitis.

Table 4. Laboratory factors among reactive lymphadenitis, kikuchi's disease and tuberculous lymphadenitis.

	Reactive Lymphadenitis mean±SD or n(%)	Kikuchi's Disease mean±SD or n(%)	Tuberculous Lymphadenitis mean±SD or n(%)	P-value
WBC (10^3/μL)	5.8±2.6	4.4±2.3	6.0±1.9	<0.001
T[a]	a	b	a	
Leukopenia*	14(17.5)	40(50.0)	8(10.0)	<0.001
Delta neutrophil	0.58±1.9	1.13±2.5	0.58±1.2	0.499
Hb (g/dL)	13.2±1.3	12.4±1.5	12.9±1.3	0.011
T[a]	a	b	a,b	
RDW	13.6±6.0	12.9±1.3	13.8±5.1	0.459
PLT (10^3/μL)	252.9±81.5	212.1±71.1	265.7±65.6	<0.001
T[a]	a	b	a	
Procalcitonin(mcg/L)	0.06±0.04	2.73±4.55	0.06±0.02	0.498
ESR (mm/hr)	34.8±29.5	45.3±28.7	34.3±29.5	0.188
CRP (mg/L)	8.7±16.0	23.1±42.5	11.9±25.0	0.091
Albumin (g/dL)	4.4±0.4	4.0±0.6	4.4±0.3	<0.001
T[a]	a	b	a	
Hypoalbuminemia**	7(8.8)	33(41.3)	8(10.0)	<0.001
CRP/albumin ratio	1.5±4.1	6.8±14.3	3.0±6.4	0.021
T[a]	a	b	a	
BUN (mg/dL)	11.0±4.0	10.3±4.3	11.4±6.2	0.358
Cr (mg/dL)	0.75±0.2	0.75±0.2	0.87±1.2	0.587
AST (IU/L)	29.6±31.6	48.6±77.1	26.1±41.2	0.033
T[a]	a	b	a	
ALT (IU/L)	32.2±54.2	35.0±53.5	23.3±60.5	0.420
Interferon-ɤ	2/5(40)	8/22(36.4)	10/12(83.3)	0.028

* Leukopenia indicates that the absolute count of leukocytes is below < 4,000/μL.

** Hypoalbuminemia indicates that the serum albumin level is below 4g/dL

Table 5. Comparison of sonographic features among reactive lymphadenitis, kikuchi's disease and tuberculous lymphadenitis.

	Reactive Lymphadenitis mean±SD or n(%)	Kikuchi's Disease mean±SD or n(%)	Tuberculous Lymphadenitis mean±SD or n(%)	P-value
Size of LN				
Long diameter	16.3±6.0	16.1±7.4	23.1±11.6	<0.001
T[a]	a	a	b	
Short diameter	7.1±3.0	7.4±3.0	12.9±6.4	<0.001
T[a]	a	a	b	
Crowding of LN				
Discrete	55(91.7)	32(97.0)	30(46.2)	<0.001
Matted	5(8.3)	1(3.0)	35(53.8)	<0.001
Shape of LN				
Oval	60(98.4)	34(100)	36(55.4)	<0.001
Round	1(1.6)	0(0)	29(44.6)	<0.001
Margin of LN				
Regular	61(100)	34(100)	33(50.8)	<0.001
Irregular	0(0)	0(0)	32(49.2)	<0.001
Echogenicity				
Homogenous	55(90.2)	33(97.1)	26(40.0)	<0.001
Heterogenous	6(9.8)	1(2.9)	39(60.0)	<0.001
Internal echogenicity				
Presence	3(4.9)	2(5.9)	13(20.0)	<0.015
Absence	58(95.1)	32(94.1)	52(80.0)	<0.015
Hypoechoic center				
Presence	0(0)	3(8.8)	59(90.8)	<0.001
Absence	61(100)	31(91.2)	6(9.2)	<0.001
Intranodal necrosis				
Presence	0(0)	0(0)	57(87.7)	<0.001
Absence	61(100)	34(100)	8(12.3)	<0.001
Number of LN				
< 5	52(82.5)	38(73.1)	34(52.3)	<0.001
≥ 5	11(17.5)	14(26.9)	31(47.4)	<0.001

6. Computed tomography imaging characteristics

Table 6. Comparison of CT findings among reactive lymphadenitis, kikuchi's disease and tuberculous lymphadenitis.

	Reactive Lymphadenitis mean±SD or n(%)	Kikuchi's Disease mean±SD or n(%)	Tuberculous Lymphadenitis mean±SD or n(%)	P-value
CT attenuation (HU)	91.0±20.9	83.6±52.8	132.6±125.4	0.05
Crowding of LN				
Discrete	48(87.3)	31(88.6)	19(27.5)	<0.001
Matted	7(12.7)	4(11.4)	50(72.5)	<0.001
Necrosis of LN				
Presence	5(9.1)	9(25.7)	63(91.3)	<0.001
Absence	50(90.9)	26(74.3)	6(8.7)	<0.001
Extent of necrosis				
Minmal	39(88.6)	27(84.4)	5(7.6)	<0.001
Marked	5(11.4)	5(15.6)	61(92.4)	<0.001
Number of necrosis				
Single	38(86.4)	25(78.1)	7(10.8)	<0.001
Multiple	6(13.6)	7(21.9)	58(89.2)	<0.001
Location of necrosis				
Central	40(90.9)	27(84.4)	60(92.3)	0.459
Peripheral	4(9.1)	5(15.6)	5(7.7)	0.459
Margin of necrosis				
Indistinct	42(95.5)	28(90.3)	61(93.8)	0.666
Well difined	2(4.5)	3(9.7)	4(6.2)	0.666
Perinodal infiltration	3/55(5.5)	7/34(20.6)	47/69(68.1)	<0.001
Calcification	0/55(0)	1/34(2.9)	9/69(13.0)	0.008

In comparison of CT findings, there were also many remarkable distinctions among three groups. In reactive lymphadenitis and kikuchi's disease, crowding

of lymph nodes was discrete comparing that it was matted in tuberculous lymphadenitis ($p<0.001$). Necrosis of lymph nodes was predominant feature of tuberculous lymphadenitis ($p<0.001$). Extent of necrosis was zero to minimal in reactive lymphadenitis and kikuchi's disease, on the contrary, there was markedly extension of necrosis in tuberculous lymphadenitis ($p<0.001$). By perspective of nodal necrosis, in reactive lymphadenitis and kikuchi's disease, there were single nodal necrosis. On the other hand, there was multiple nodal necrosis in tuberculous lymphadenitis ($p<0.001$). Furthermore, perinodal infiltration ($P<0.001$) and calcification ($P=0.008$) were interesting point of tuberculous lymphadenitis in computed tomography images.

However, there were no differences in location and margin of nodal necrosis among three groups. Most patients had a central location of necrosis and indistinct margin of necrosis.

7. Multivariate analysis

And then, we made a multivariate analysis among three groups. Between kikuchi's disease and reactive lymphadenitis, fever (OR 9.69) and leukopenia (OR 3.11) were predictive factors. It means, if the patients have a fever or leukopenia, risk of reactive lymphadenitis is increasing rather than kikuchi's disease. According to multivariate analysis between reactive and tuberculous lymphadenitis, there were three significant predictive factors. That were headache (OR 28.04), leukopenia (OR 17.74) and CRP/albumin ratio (OR 9.60). So, when the patients who suffering from headache or having lower serum leukocytes level or higher CRP/albumin level visit hospital, the risk of reactive lymphadenitis increase than tuberculous lymphadenitis. Similarly, by multivariate analysis between kikuchi's disease and tuberculous lymphadenitis predictive factors were fever (OR 10.17), leukopenia (OR 8.88) and hypoalbuminemia (OR 3.25).

Table 7. Multivariate analysis of predictive factors for kikuchi's disease comparing with reactive lymphadenitis

Variables	Odds ratio (95%CI)	P-value
Fever	9.69 (3.25 – 28.88)	<0.001
Leukopenia*	3.11 (1.09 – 8.87)	0.034

* The reference point of leukopenia is 4,000/μL

Table 8. Multivariate analysis of predictive factors for reactive lymphadenitis comparing with tuberculous lymphadenitis.

Variables	Odds ratio (95%CI)	P-value
Headache	28.04 (1.83 – 428.01)	0.016
Leukopenia*	17.74 (1.33 – 235.81)	0.029
CRP/albumin ratio**	9.60 (1.02 – 90.08)	0.048

* The reference point of leukopenia is 4,000/μL

** The reference point of CRP/albumin ratio is 2.0

Table 9. Multivariate analysis of predictive factors for kikuchi's disease comparing with tuberculous lymphadenitis.

Variables	Odds ratio (95%CI)	P-value
Fever	10.17 (3.47 – 29.80)	<0.001
Leukopenia*	8.88 (3.05 – 25.87)	<0.001
Hypoalbuminemia***	3.25 (1.03 – 10.28)	0.044

* The reference point of leukopenia is 4,000/μL

*** The reference point of albumin is 4g/dL

IV. DISCUSSION

Cervical lymphadenitis is common disease and needs careful access when we make a decision for diagnosis initially. The disease spectrum and prognosis are variable, so we have to evaluate and examine the three disease groups observantly.

All the study members had a biopsy process, the reason of different biopsy technique is correlates with severity of the disease. Reactive lymphadenitis is relatively considered as a slight disease, so the patients have a tendency of gradational biopsy technique like less invasiveness to invasiveness. And most patients of kikuchi's disease had a fever (68.8%) and long duration of fever (11.7±11.9), so histopathologic result is very important. So they have a tendency to have an excisional biopsy rather than less invasive biopsy techniques. Also this theory can be applied to tuberculous lymphadenitis.

Song JY et al suggest that common anatomical locations of lymph nodes were significant different among three groups. Level V was dominant in reactive lymphadenitis, level III and V were prominent in kikuchi's disease and level II, III, IV were prominent in tuberculous lymphadenitis.[6] According to our review, the results show inconsistency. In reactive lymphadenitis, level II and III were prominent area and 50% to 53.8% patients of kikuchi's disease had a prominent area at level III and IV. In tuberculous lymphadenitis, also prominent area were level III and IV, likewise around jugular chain.

And Elias Campo et al, described no specific laboratory test is available for diagnosing kikuchi's disease. The majority of patients with kikuchi's disease have a normal range of complete blood count.[14] They said some of the patients have anemia, a slight elevated erythrocyte sedimentation rate (ESR) and serum lactate dehydrogenase. Mild leukopenia has been observed in 25% to 58% of patients. But, in our data, leukopenia (leukocyte<4000g/dL) was seen in 40 patients (50%) of kikuchi's disease, anemia (hemoglobin<12g/dl) was seen in 30 patients (37.5%) and thrombocytopenia (platelet<150K) was seen in 10

patients (12.5%). And elevated of ESR was also seen, but there was no statistical significance (p=0.188). Furthermore, serum level of aspartate aminotransferase (AST) was increased in kikuchi's disease. Hypoalbuminemia was seen in 33 patients (41.3%), C-reactive protein(CRP)/albumin ratio was elevated, mean ratio was 6.8±14.3 comparing that it was 1.5±4.1 in reactive and 3.0±6.4 in tuberculous lymphadenitis. We couldn't analyze serum lactate dehydrogenase because there were few cases.

The mechanism of cytopenia in kikuchi's disease has been studied using an in vitro culture system. By Dorfman RF et al, one or more inhibitory factors might cause granulocytopenia in patients with kikuchi's disease.[15] And the etiology of kikuchi's disease was not clearly known, some of viral infection or autoimmune diseases are correlate with kikuchi's disease and then it can cause elevation of serum aspartate aminotransferase.

Whole-body interferon-gamma enzyme-linked immune sorbent assay (QFT) is also helpful for the diagnosis of cervical tuberculosis, but interferon-gamma alone is not sufficient for diagnosis of extra-pulmonary tuberculosis.[16] In our data, 10 of 12 patients (83.3%) of tuberculous lymphadenitis had positive value for interferon-gamma, but the case was too small to additional analyze. So, diagnostic value of interferon-gamma needs more data review.

Considering radiologic features, sonographic findings are distinctive with reactive and kikuchi's disease. Most of sonographic features are concretely distinguishable as crowding, shape, margin, echogenicity, necrosis and number of lymph nodes ($p<0.001$). Adversely, in tuberculous lymphadenitis there were a few distinctive sonographic features, only presence of hypoechoic center and intra nodal necrosis could be predictive factors of tuberculous lymphadenitis.

All the more, CT image was good predictive factors of tuberulous lymphadenitis. Crowding and margin of lymph nodes were more distinctive by CT image than sonographic review. Presence of necrosis and perinodal infiltration were also distinguishable features of tuberculous lymphadenitis than

other two diseases. But radiologic predictive factors between reactive disease and kikuchi's disease are very faint. So we recommend the clinical and laboratory results such as weight loss, headache, fatigue and complete blood cell count must be checked for differential diagnosis between reactive and kikuchi's disease.

By multivariate anaylsis using logistic regression, leukopenia was most important predictive factor. And also CRP/albumin ratio, serum albumin level, fever and headache should be checked.

V. CONCLUSION

In conclusion, our results indicate that different factors among three groups are distinctive. So, when we first see the patients who suffering from cervical node swelling or pain, we have to review the clinical symptoms and have to check the complete blood count, CRP, albumin. And then ultrasound-guided biopsy must be done for early differential diagnosis of cervical lymphadenitis.

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ABSTRACT(IN KOREAN)

경부 임파선염에서 조기 진단을 위한 임상적, 혈청학적 그리고 영상학적 진단요소

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이경화

경부 임파선염은 여러 형태의 서로 다른 질환으로 구성된다. 각 질환의 치료 방법과 예후는 다양하게 나타난다. 따라서 본 연구는 흔한 경부 임파선염인 반응성 임파선염, 조직구 괴사성 임파선염(Kikuchi’s disease)그리고 결핵성 임파선염에서 서로 다른 요인이 무엇인지 평가하는데 목적을 두고자 한다.

3차 의료기관인 강남 세브란스병원에 2005년 5월부터 2014년 11월 사이에 내원한 임파선염 환자의 의무기록을 후향적으로 점검하였고 이들 세 군 간의 임상적, 혈청학적 그리고 영상학적 차이점을 비교하였다.(각 그룹의 모수는 80명 이었다.)

본 연구에서 총 240명의 환자가 모집 되었고 이들의 평균 나이는 36.9세 이었다. 발열기간이 길 수록, 백혈구, 헤모글로빈, 혈소판, 알부민 수치가 낮을수록, 혈청 AST 수치가 높을수록 다른 두 질환 보다 조직구 괴사성 임파선염의 유의미한 특징을 나타내었다. 그리고 경부 종물은 반응성 임파선염과 결핵성 임파선염의 주요한 초기 증상

이었고 이에 반해 조직구 괴사성 임파선염에서는 경부 부종과 발열이 주요한 초기 증상이었다. 또한 발열, 체중감소, 피로감, 두통은 조직구 괴사성 임파선염에서 흔한 임상적 증상이었다. 해부학적으로는 반응성 임파선염에서는 II 번 구역, 조직구 괴사성 임파선염과 결핵성 임파선염에서는 III번과 IV번 구역에서 우세한 위치를 나타내었다.

영상학적 소견을 살펴보면, 경부 초음파에서 분리되어있고, 구형이면서 규칙적인 가장자리를 가진, 동일한 밀도를 가진 임파선이 반응성 임파선염과 조직구 괴사성 임파선염에서 나타났고 반대로 저 에코성 중심이나 림프절 중심 괴사부는 결핵성 임파선염의 특징이었다. 컴퓨터 단층 촬영에서는 군집되어있고, 다발성 괴사부와 주변부 침투가 있으며 석회화가 동반된 것이 결핵성 임파선염의 특징 이었다.

마지막으로 세 그룹간에 다변량 분석을 시행하였고 발열과 호중구 감소는 반응성 임파선염과 비교하였을 때 조직구 괴사성 임파선염의 예측 인자 였으며 호중구 감소와 C-반응성 단백질/알부민 비, 두통 동반은 결핵성 임파선염에 대한 반응성 임파선염의 예측인자였다. 발열, 호중구 감소, 저 알부민혈증은 결핵성 임파선염과 비교하였을 때 조직구 괴사성 임파선염의 예측인자 이었다.

본 연구에서 얻은 지식은 경부 임파선염 의심 환자를 만났을 때 조기 진단 할 수 있는 예측 인자로 도움이 될 것이다.

핵심되는 말 : 경부 임파선염, 반응성 임파선염, 결핵성 임파선염, 조직구 괴사성 임파선염