

The predictive value of epidemiological characteristics, clinical and laboratory findings in adult lymphadenopathy etiology

S. AKINCI¹, K. SILAY², T. HACIBEKIROGLU¹, A. ULAS³, A. BASTURK¹, S.M. BAKANAY¹, M.B. AKINCI³, A. YIKILMAZ¹, I. DILEK¹

¹Department of Hematology, Ankara Ataturk Training and Research Hospital, Ankara, Turkey

²Department of Geriatrics, Yildirim Beyazit University, Ankara, Turkey

³Department of Oncology, Yildirim Beyazit University, Ankara, Turkey

Abstract. – OBJECTIVE: Our aim was to determine the presence or absence of malignant etiology in the epidemiological, clinical and laboratory results of patients undergoing lymph node biopsies.

PATIENTS AND METHODS: This study was carried out between January 2013 and April 2014. We enrolled a total of 150 adult patients who had lymph node biopsies. 73 of these were females (48.7%) and 77 were males (51.3%). The epidemiological characteristics, clinical and laboratory findings were evaluated and compared with the pathological results.

RESULTS: Leukopenia ($p=0.05$) thrombocytopenia ($p=0.03$) and increased lactate dehydrogenase levels ($p=0.01$) were found to be associated with the malignancy. In the cervical, submandibular, axillary and inguinal areas lymphadenopathy was generally seem to be benign while the rate of malignancy was higher in the intra-abdominal and supraclavicular regions. In those cases who had a lymph node index of below 2 there was a higher rate of malignancy ($p=0.04$). In cases which lymphadenopathy accompanied by splenomegaly has been found associated with malignancy ($p=0.009$). No association with regards to malignancy was found with the erythrocyte sedimentation rate, C-reactive protein and hepatomegaly.

CONCLUSIONS: According to the results of the study five variables including cytopenia, lactate dehydrogenase levels, splenomegaly, lymph node index below 2, intra-abdominal and supraclavicular lymphadenopathy were concluded to be the most suitable means of predicting malignant etiology.

Key Words:

Lymphadenopathy, Cytopenia, Malignancy, Splenomegaly.

ing the course of examinations for completely different reasons. It is at that moment that any signs or symptoms will require the intervention of a health care provider. The physician then has to decide whether or not the lymphadenopathy (LAD) is normal or whether further investigations may be required including biopsy. Taking a detailed history, doing necessary laboratory tests and performing a thorough physical examination will help the physician to evaluate the LAD¹⁻⁴. All of the patients in this study were admitted to our clinic and lymph node biopsies were performed. The patients' demographic characteristics, clinical and laboratory results were then carefully evaluated.

Patients and Methods

This study carried out between January 2013 and April 2014; a total of 150 patients who had underwent LAD biopsy were enrolled. There were 73 females (48.7%) and 77 males (51.3%). Our exclusion criteria were patients who had had a previous diagnosis of malignancy and, therefore, had received either chemotherapy or radiotherapy. We recorded the patients' age and gender characteristics along with their hemogram parameters, leukocyte, platelet count, concomitant presence of hepatomegaly and splenomegaly, the location of the lymph nodes (cervical, submandibular, supraclavicular, axillary, inguinal, intra-abdominal), lymph node diameter, pathological diagnosis, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and lactate dehydrogenase (LDH) values. In the ESR assessment for woman $(age+10)/2$ and for men $age/2$ the values were determined according to the rules, high and low values were calculated ac-

Introduction

Lymphadenopathy is a common clinical sign. It may be revealed, as an incidental finding, dur-

cordingly⁵. For size criteria of the nodes, the longitudinal diameter and the transverse diameter were considered and the ratio of the former to the latter was calculated to obtain Solbiati Index⁶. Two groups were then established in relation to whether the (lymph node) index as 2 or over or rather as below 2.

Statistical Analysis

Patients were statistically divided into two groups according to whether their pathological diagnosis showed as benign or malignant. SPSS 17.0 programme (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. Numerical data were expressed as $\pm$ mean standard deviation. In addition to numerical data all frequency analysis was given in percentages. Chi-square test was used to perform statistical analysis relating to the presence or absence of malignancy subsequent to the lymph node pathology results. $p < 0.05$ was considered statistically significant.

Results

A total of 150 patients were enrolled in our study. Of these 73 were female (48.7%) and 77 were male (51.3%). According to the patients' hemogram parameters there were found to be 44 (29.3%) cases of anemia, 14 (9.3%) of leukopenia, 16 (10.7%) with leukocytosis, 21 (14%) with thrombocytopenia and 7 (4.7%) with thrombocytosis. In this study there were 81 (54%) cases where the ESR values were seen to be high in comparison with the normal for their age group. 69 (46%) patients were found to have high LDH values and a further 69 (46%) patients had increased CRP levels. 82 patients (54.7%) were below 2 on the lymph node index whereas 68 (45.3%) were at 2 or above on the same index scale. The distribution of patients LAD based on localization and frequency can be seen in Table I. Malignancy was present in a total of 42 cases (27.3%) while 108 cases (72.7%) were found to be benign. The pathological diagnosis of all cases can be seen in Table II.

The pathological diagnosis of malignant cases were diffuse large B cell lymphoma (37.5%), metastatic carcinoma (32.5%), Hodgkin's lymphoma (20%), mantle cell lymphoma (5%), chronic lymphocytic leukemia (2.5%), follicular lymphoma (2.5%) and schwannoma (2.5%).

A total of 8 cases (5.3%) were found to have hepatomegaly. 4 (2.7%) of these were benign and

Table I. The distribution of patients LAD based on localization and frequency.

Lymph node location	Number (n)
Cervical	53 (35.3%)
Axillary	53 (35.3%)
Inguinal	28 (18.7%)
Submandibular	9 (6%)
Supraclavicular	4 (2.7%)
Intra-abdominal	3 (2%)

the remaining 4 (2.7%) were malignant. There was no significant association between malignancy and hepatomegaly ($p=1.215$). 12 out of 41 patients (29.3%) with a malignancy diagnosis together with 11 out of the total 109 patients with a benign diagnosis were found to have splenomegaly. Therefore, there was seen to be a statistically significant association between splenomegaly and malignancy ($p=0.009$). A limited association between anemia and malignancy was also found ($p=0.069$). In the study the presence of leukopenia and thrombocytopenia was also linked to malignancy ($p=0.056$), ($p=0.031$) (Table III).

There was no significant relationship between malignancy and CRP and ESR ($p=0.466$, $p=0.582$) respectively. LDH levels were high in 63.4% of cases showing malignancy while LDH levels were normal in the remaining 36.6% of cases. In this way an association between high LDH levels and the presence of malignancy was observed ($p=0.01$). 68.3% of patients had a lymph node index rating below 2, while the remaining 31.7% were found to have an index rat-

Table II. The pathological diagnosis of all cases.

Pathological diagnosis	Number (n)
Normal	47 (31.3%)
Reactive lymph node	35 (23.3%)
Lymphoma	26 (17.3%)
Metastasis	13 (8.7%)
Granulomatous reaction	11 (7.3%)
Chronic lymphadenitis	8 (5.3%)
Non-diagnostic	3 (2%)
Abscess	2 (1.3%)
Kikuchi syndrome	1 (0.7%)
Sinus histiocytosis	1 (0.7%)
Lipoma	1 (0.7%)
Chronic lymphocytic leukemia	1 (0.7%)
Schwannoma	1 (0.7%)

Table III. The relationship between anemia, leukopenia, thrombocytopenia and the presence of malignancy in patients.

Benign	Malign	Total	Significance
Absence of anemia	82 (75.2%)	24 (58.5%)	106 (70.7%)
Anemia	27 (24.8%)	17 (41.5%)	44 (29.3%)
Absence of leukopenia	90 (92.8%)	29 (80.6%)	119 (89.5%)
Leukopenia	7 (7.2%)	7 (19.4%)	14 (10.5%)
Absence of thrombocytopenia	93 (89.4%)	28 (73.7%)	121 (85.2%)
Thrombocytopenia	11 (10.6%)	10 (26.3%)	21 (14.8%)

ing of 2 or over. It can be concluded that a lymph node index rating below 2 would suggest the presence of malignancy ($p=0.045$).

A relationship was observed between the presence of malignancy and the location of the lymph node ($p=0.04$). It was determined that in the cervical, submandibular, axillary and inguinal sites LAD was benign while there was a tendency toward malignancy in intraabdominal and supraclavicular LAD (Table IV).

Discussion

Despite the fact that most LAD appears to be benign, they may signal malignant disease. The most worrisome situation that both doctors and patients may face is that when LAD indicates such a serious condition there is always the possibility of a malignancy. Physicians need to take a careful and detailed history, do a thorough physical examination and laboratory tests as well as perform a lymph node biopsy in order to achieve an accurate evaluation⁷⁻¹⁰. In our knowledge this is among the few studies including adult population with LAD. The present study suggests important parameters for the prediction of malignant etiology in LAD cases such as considering the demographic characteristics, looking at the relationship between the clinical, laborato-

ry and biopsy results. We have concluded that in adult patients presenting with LAD, such results as cytopenias (leukopenia, thrombocytopenia), LDH levels, the presence of splenomegaly, lymph node index below 2, intra-abdominal and supraclavicular LAD can be used to accurately predict malignant etiology.

The diagnosis of benign or malignant LAD in patients may be based on varying criteria. One of these is a three variable model. The first variable is an abnormal chest X-ray. The second is if the lymph node size is greater than 2 cm. Finally the third is to evaluate ear, nose and throat symptoms. The use of these three variables in combination in patients (age between 9 and 25 years) enable us to estimate biopsy requirements in 97% of cases¹¹. In another model we use six variables (age, tenderness, lymph node size, supraclavicular location, texture and generalized pruritus) to distinguish benign versus malignant LAD^{12,13}. In this study variables such as the presence of cytopenia (denoted by leukopenia and thrombocytopenia), elevated LDH levels, the presence of splenomegaly, lymph node index below 2, intra-abdominal or supraclavicular LAD were all found to be associated with the presence of malignancy.

Lymphadenopathy is most frequently observed in the neck and head region. Differential diagnosis of LAD is extremely difficult. Malignancies

Table IV. The relationship between the location of the lymph node and the presence of malignancy.

Location of lymph node	Benign	Malign	Total
Cervical	36 (69.2%)	16 (30.8%)	52 (34.4%)
Submandibular	7 (77.8%)	2 (22.2%)	9 (6%)
Axillary	38 (71.7%)	15 (28.3%)	53 (35.6%)
Inguinal	25 (89.3%)	3 (10.7%)	28 (18.8%)
Intra-abdominal	1 (33.3%)	2 (66.7%)	3 (2%)
Supraclavicular	1 (25%)	3 (75%)	4 (2.7%)
Total	108 (72.5%)	42 (27.5%)	150 (100%)

are most commonly seen in cervical and supraclavicular LAD⁷. This study we have tried to investigate the relationship between the lymph node location and malignancy. It was found that intra-abdominal and supraclavicular malignancy rates were high; 66.7% intra-abdominal and 75% supraclavicular respectively. There is a high risk of malignancy in supraclavicular LAD and, therefore, early biopsy should be considered independently of the size^{14,15}. Looking at further studies, supraclavicular LAD malignancy has been detected in some 34-50% of cases. It has been found that the risk was great age of forty^{16,17}. The fact that in our study the frequency of malignancy in supraclavicular and intra-abdominal LAD was not very high may be due to the relatively lower number of our patients.

When evaluating the hemogram parameters of our patients it was discovered that 29.3% had anemia, 9.3% had leukopenia and 14% thrombocytopenia. Hemograms of patients with LAD have shown that the presence of such abnormalities as anemia, leukopenia and thrombocytopenia are likely to increase the incidence of malignancy. One of the study it was observed that patients with malignancies had a higher prevalence of anemia, thrombocytopenia, leukocyte, mediastinal or hilar LAD when compared to benign cases¹⁸. There is limited observed data available on this subject in general literature.

The ESR, CRP and LDH levels are not specific and usually related to infection or inflammation. In literature, hepatosplenomegaly, mediastinal LAD, systemic symptoms and increased LDH levels have all been associated with malignancy¹⁹. In our study, a significant association was found between high LDH levels and the presence of malignancy. Sedimentation and CRP were found to be high in approximately half of the patients in the study group. There was no direct association between malignancy and sedimentation and CRP levels. The high ESR and CRP level was interpreted as an acute phase reactant since the biopsy results has showed high rate of reactive lymphoma, metastasis, chronic lymphadenitis or granulomatous reaction.

One of the important criteria in the differentiation of benign and malignant LAD concerns the lymph node diameter. In our study we use the Solbiati lymph node index to calculate the ratio of large and small diameter lymph nodes⁶. Generally, the rounded nodes carry higher suspicion of malignancy in comparison with oval shaped nodes. In the LAD area, series of evaluations of LAD were

used. It was found that when under 1 cm² there was no evidence of malignant LAD in patients. Between 1-2.25 cm² 8% of the patients had malignant LAD and 38% had malignancy when the node was greater than 2.25 cm² in size²⁰. In a study the ratio of 1 to share diameter reactive lymph nodes was found to be over to 86% of the cases²¹. It was emphasized that the LAD shape minimal axial diameter in combination with minimal axial diameter criteria increases accuracy. It has been observed that the malignant LAD has a low Solbiati index score (average 1.5) while the benign LAD has a high index score (average 2.4)⁶. Our study is compatible with literature in the incidence of malignancy was higher in those patients with a lymph node index below 2.

LAD is detected in a significant number of hematologic malignancies. Likewise it is seen in an important portion of clinical splenomegaly²². In literature has reported that 449 patients with a prevalence of 27% had hematologic malignancies²³. A study splenomegaly found an 18% prevalence of hematologic malignancy²⁴. In our study into LAD etiology it was noticed that there was an increased rate of malignancy in patients with splenomegaly (29.3% malign cases compared to 10.1% benign cases). As can be seen from these results there is increased probability of malignancy when LAD is accompanied by splenomegaly.

Conclusions

We suggest that as far as LAD patients results is concerned five variables including cytopenia, increased LDH, splenomegaly, lymph node index rating of 2 or above, the presence of intra-abdominal and supraclavicular lymphadenopathy might be the most suitable predictor between benign and malignant etiology.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

- 1) KELLY CS, KELLY RE. Lymphadenopathy in children. *Pediatr Clin North Am* 1998; 45: 875-888.
- 2) JACKSON MA, CHESNEY PJ. Lymphatic system and generalized lymphadenopathy. In: *Principles and Practice of Pediatric Infectious Diseases*, 4th ed,

- Long SS, Pickering LK, Prober CG, Elsevier Saunders, Edinburg, 2012; p. 127.
- 3) CHAU I, KELLEHER MT, CUNNINGHAM D, NORMAN AR, WOTHERSPOON A, TROTT P, RHYS-EVANS P, QUERCI DELLA ROVERE G, BROWN G, ALLEN M, WATERS JS, HAQUE S, MURRAY T, BISHOP L. Rapid access multidisciplinary lymph node diagnostic clinic: analysis of 550 patients. *Br J Cancer* 2003; 88: 354-361.
- 4) AMADOR-ORTIZ C, CHEN L, HASSAN A, FRATER JL, BURACK R, NGUYEN TT, KREISEL F. Combined core needle biopsy and fine-needle aspiration with ancillary studies correlate highly with traditional techniques in the diagnosis of nodal-based lymphoma. *Am J Clin Pathol* 2011; 135: 516-524.
- 5) MILLER A, GREEN M, ROBINSON D. Simple rule for calculating normal erythrocyte sedimentation rate. *Br Med J (Clin Res Ed)* 1983; 286: 266.
- 6) SOLBIATI L, CIOFFI V, BALLARATI E. Ultrasonography of the neck. *Radiol Clin North Am* 1992; 30: 941-954.
- 7) SAIFULLAH MK, SUTRADHAR SR, KHAN NA, HAQUE MF, HASAN I, SUMON SM, ISLAM MZ, RAHMAN S, BARMAN TK, RAHMAN A, DATTA PK, FERDOUS J, CHOWDHURY SA, MIAH AH, PANDIT H. Diagnostic evaluation of supraclavicular lymphadenopathy. *Mymensingh Med J* 2013; 22: 8-14.
- 8) NIEDZIŁSKA G, KOTOWSKI M, NIEDZIŁSKI A, DYBIEC E, WIECZOREK P. Cervical lymphadenopathy in children-incidence and diagnostic management. *Int J Pediatr Otorhinolaryngol* 2007; 71: 51-56.
- 9) ABDEL RAZEK AA, SOLIMAN NY, ELKHAMARY S, ALSHARAWAY MK, TAWFIK A. Role of diffusion-weighted MR imaging in cervical lymphadenopathy. *Eur Radiol* 2006; 16: 1468-1477.
- 10) MRÓWKA-KATA K, KATA D, KYRCZ-KRZEMIE S, HELBIG G. Kikuchi-Fujimoto and Kimura diseases: the selected, rare causes of neck lymphadenopathy. *Eur Arch Otorhinolaryngol* 2010; 267: 5-11.
- 11) SLAP GB, BROOKS JS, SCHWARTZ JS. When to perform biopsies of enlarged peripheral lymph nodes in young patients. *JAMA* 1984; 252: 1321-1326.
- 12) GLICK RD, PEARSE IA, TRIPPE T, SAENZ NC, GINSBERG RJ, LA QUAGLIA MP. Diagnosis of mediastinal masses in pediatric patients using mediastinoscopy and the Chamberlain procedure. *J Pediatr Surg* 1999; 34: 559-564.
- 13) KHANNA R, SHARMA AD, KHANNA S, KUMAR M, SHUKLA RC. Usefulness of ultrasonography for the evaluation of cervical lymphadenopathy. *World J Surg Oncol* 2011; 9: 29.
- 14) RABINOWITZ MR, LEVI J, CONARD K, SHAH UK. Castleman disease in the pediatric neck: a literature review. *Otolaryngol Head Neck Surg* 2013; 148: 1028-1036.
- 15) IACONETTA G, FRISCIA M, DELL'AVERSANA ORABONA G, DE BIASI S, ROMANO A, PIOMBINO P, GRAZIANO P, ABBATE V, SALZANO G, MAGLITTO F, CALIFANO L. Castleman's disease mimicking a parotid gland tumor: report of a case and review of the literature. *Eur Rev Med Pharmacol Sci* 2014; 18: 1241-1246.
- 16) FIJTEN GH, BLIJHAM GH. Unexplained lymphadenopathy in family practice. An evaluation of the probability of malignant causes and the effectiveness of physicians' workup. *J Fam Pract* 1988; 27: 373-376.
- 17) CHAU I, KELLEHER MT, CUNNINGHAM D, NORMAN AR, WOTHERSPOON A, TROTT P, RHYS-EVANS P, QUERCI DELLA ROVERE G, BROWN G, ALLEN M, WATERS JS, HAQUE S, MURRAY T, BISHOP L. Rapid access multidisciplinary lymph node diagnostic clinic: analysis of 550 patients. *Br J Cancer* 2003; 88: 354-361.
- 18) KUMRAL A, OLGUN N, UYSAL KM, CORAPCIO LU F, OREN H, SARIALIO LU F. Assessment of peripheral lymphadenopathies: experience at a pediatric hematology-oncology department in Turkey. *Pediatr Hematol Oncol* 2002; 19: 211-218.
- 19) YARIS N, ÇAKIR M, SÖZEN E, COBANOGU U. Analysis of children with peripheral lymphadenopathy. *Clin Pediatr (Phila)* 2006; 45: 544-549.
- 20) YU M, LIU Q, SONG HP, HAN ZH, SU HL, HE GB, ZHOU XD. Clinical application of contrast-enhanced ultrasonography in diagnosis of superficial lymphadenopathy. *J Ultrasound Med* 2010; 29: 735-740.
- 21) PANGALIS GA, VASSILAKOPOULOS TP, BOUSSIOTIS VA, FESSAS P. Clinical approach to lymphadenopathy. *Semin Oncol* 1993; 20: 570-582.
- 22) HEMATOLOGICAL EVALUATION OF SPLENOMEGALY. ALI N, ANWAR M, AYYUB M, NADEEM M, EJAZ A, QURESHI AH, QAMAR MA. *J Coll Physicians Surg Pak* 2004; 14: 404-406.
- 23) BRUNETON JN, BALU-MAESTRO C, MARCY PY, MELIA P, MOUROU MY. Very high frequency (13 MHz) ultrasonographic examination of the normal neck: detection of normal lymph nodes and thyroid nodules. *J Ultrasound Med* 1994; 13: 87-90.
- 24) O'REILLY RA. Splenomegaly in 2,505 patients at a large university medical center from 1913 to 1995. 1963 to 1995: 449 patients. *West J Med* 1998; 169: 88-97.