Risk analysis in persistent cervical lymphadenopathies: Malignant or benign?

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ABSTRACT

OBJECTIVE: The objective of the study was to determine the parameters that can be used to predict malignancy in persistent cervical lymphadenopathies.

METHODS: We retrospectively reviewed the files of 162 patients diagnosed with persistent cervical lymphadenopathy who underwent an excisional biopsy in our department between January 2011 and October 2019. Patient demographics and the size, side, duration, and localization of lymphadenopathy were recorded, and their relationship with histopathological results was investigated. Multiple regression analysis was used to determine the relationship between clinical parameters and malignancy.

RESULTS: Of the 162 patients, 91 (56.2%) were male and 71 (43.8%) were female, and the mean age was 45.40±20.41 (2–84) years. Male gender (OR=3.099; p=0.003), increasing age (OR=1.029; p=0.002), short duration of lymphadenopathy (OR=0.989; p=0.048), and neck level V (OR=2.604; p=0.031) patients had a statistically significantly higher risk of malignancy. There was no statistically significant relationship between the side and size of the lymph node and the risk of malignancy (p>0.05).

CONCLUSION: In our study, male gender was determined to be the most predictive risk factor for malignancy in patients with cervical lymphadenopathy, followed by lymph node neck level, increased age, and duration of the disease.

Keywords: Biopsy; lymphadenopathy; malignancy.

Lymphadenopathy (LAP) is defined as an abnormality in the size and characteristics of a given lymph node. LAP results from the proliferation of neoplastic or inflammatory cells in the lymph node. LAP can be caused by infectious diseases (e.g., viral, bacterial, fungal, and parasitic), some non-infectious diseases (e.g., sarcoidosis, connective tissue disorders, etc.), lymphoproliferative diseases, and other infiltrative malignant diseases [1].

In both adults and children, enlarged cervical lymph nodes are mostly benign and tend to regress spontaneously or by treatment. However, a biopsy is required for diagnosis, especially in cases that do not regress with antibiotic therapy or if a systemic disease is suspected. Although fine-needle aspiration biopsy is useful in benign-malignant differentiation, it often fails to establish a definitive diagnosis [2]. Furthermore, excisional biopsy is required for the diagnosis of lymphoma [3, 4]. In the diagnosis of persistent LAP, excisional biopsy is the gold standard diagnostic method, and it can be safely performed with minimal morbidity and mortality [5, 6]. However, the most important problem facing the diagnosis of LAP is determining the most appropriate can-

didate and time point for excisional biopsy. To prevent unnecessary surgery on the patient and to detect malignancy as early as possible, understanding and recognizing the symptoms of LAP malignancy are crucial.

The present study aims to compare clinical and histopathological data of patients who had undergone excisional biopsy in our department to determine the parameters that can be used to predict malignancy in persistent cervical LAPs.

MATERIALS AND METHODS

We retrospectively analyzed the files of patients diagnosed with persistent cervical LAP who had undergone an excisional biopsy in the ear, nose, and throat (ENT) department of Pamukkale University Hospital between January 2011 and October 2019. Lymph nodes with a diameter exceeding 1 cm, that are unresponsive to antibiotic treatment, and that have not regressed for a period exceeding 3 weeks, were considered "persistent LAP" in our study.

Patients were excluded from the study if a primary disease had already been established or if detailed history and surgery notes were inaccessible. A total of 162 patients met the inclusion criteria and were included in the study. Demographic data and the size, duration, and localization of LAP were recorded, and their relationship with histopathological results was investigated. Patient ages were stratified into three groups: <18 years, 18–40 years, and >40 years. Likewise, lymph node size was classified as either <3 cm or ≥3 cm. Lymph node localizations were evaluated according to sides and neck levels. The duration of the enlarged lymph node was determined according to the first symptom date reported by the patients. The parameters that could be used to predict LAP malignancy were determined from these data.

Ethics committee approval was obtained from the Pamukkale University clinical research ethics committee (60116787-020/54307).

Statistical Analysis

The data were analyzed with SPSS version 24.0 software (IBM Corporation, Armonk, NY, USA). Continuous variables were expressed as mean±standard deviation and range, and categorical variables were expressed as Arabic numerals and percentages. The Student's t-test was used for comparison between two groups, and the Chi-square test was used for categorical group compar-

Highlight key points

- Male gender was determined to be the most predictive risk factor for malignancy in patients with cervical lymphadenopathies.
- Neck level V was associated with a 2.6 times higher risk for malignancy than the other neck levels.
- Increased age was significantly associated with malignancy.
- As the duration of the disease increases, the likelihood of lymphadenopathy being malignant decreases.

isons. Multiple logistic regression models were used for predictions of various factors. The statistical significance level was set at p<0.05.

RESULTS

Of the 162 patients, 91 (56.2%) were male and 71 (43.8%) were female, a male-to-female ratio of 1.3:1. The mean age was 45.40±20.41 (min.–max.: 2–84) years. Patient demographics and clinical characteristics are shown in Table 1. Furthermore, 98 of the 162 LAPs (60.5%) were benign, while 64 (39.5%) were malignant. Histopathological results are summarized in Figure 1. The most frequent benign lesion was reactive lymphadenitis, whereas the most frequent malignant lesion was lymphoma.

When analyzing the relationship between gender and malignancy, malignancy rates were observed in 23.9% of female patients and 51.7% of male patients. Malignant lesions were significantly higher in males than in females (p=0.002).

Lymph node excision was performed on the right side on 71 (43.8%) patients and on the left side in 91 (56.2%) patients. No significant correlations were found between lymph node location and malignancy (p>0.05).

The patients were categorized according to three age groups: <18 years (pediatric age group), 18–40 years, and >40 years. Malignancy rates were 13.6% in patients aged <18 years, 32.4% in those aged 18–40 years, and 47.2% in patients aged >40 years. Malignant lesions were significantly correlated to patients aged >40 years (p=0.009).

The LAP size was categorized as either <3 cm or ≥3 cm. Malignancy rates of 35% were found in patients with LAP size <3 cm and 46.8% in those with LAP size ≥3 cm. Although higher malignancy rates were observed in the LAP size ≥3 cm group, no statistically significant relationship was found between lymph node size and malignancy (p>0.05).
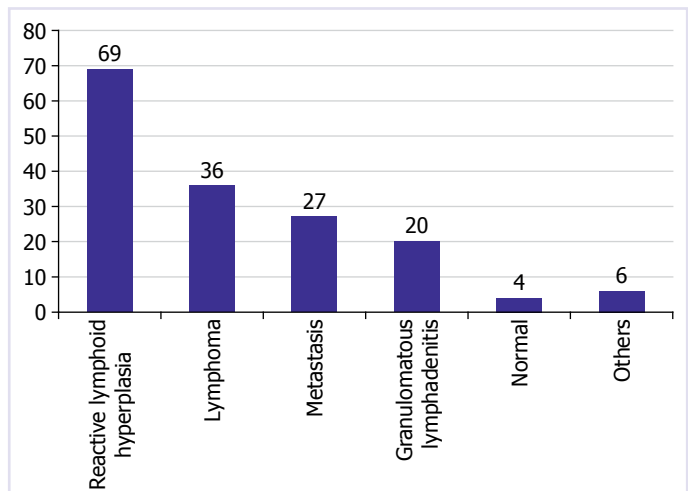
TABLE 1. Demographic and clinical data of the patients

		Total	Benign	Malignant	p
Gender, %	n				0.002*
	Male	91	48.3	51.7	
	Female	71	76.1	23.9	
Age (years), %	n				0.009*
	<18	22	86.7	13.6	
	18–40	34	67.6	32.4	
	>40	106	52.8	47.2	
Side, %	n				0.178
	Right	71	64.8	35.2	
	Left	91	57.2	42.8	
Size, %	n				0.136
	<3 cm	100	65.0	35.0	
	≥3 cm	62	53.2	46.8	
Duration (weeks)			8.30±7.18	7.05±5.38	0.016*
Neck level, %	n				0.029*
	Level I	4	75.0	25.0	
	Level II	36	66.7	33.3	
	Level III	54	74.1	25.9	
	Level IV	34	50.0	50.0	
	Level V	34	41.2	58.8	

*: P<0.05 the statistical significance level.

FIGURE 1. The histopathological distribution of the lymph nodes.

TABLE 2. Results of multivariate analysis of malignancy parameters

Variables	p	OR	95% CI for OR	
			Lower	Upper
Gender	0.003*	3.099	1.444	6.375
Age	0.002*	1.029	1.010	1.049
Neck level (level V)	0.031*	2.604	1.093	6.200
Duration	0.048*	0.989	0.978	1.000
Size	0.739	1.039	0.829	1.303

CI: Confidence interval; OR: Odds ratio; *: P<0.05 the statistical significance level.

The duration of LAPs was examined in two groups according to the histopathological characteristics: Benign and malignant. In the benign group, the mean duration of the enlarged LAP was 8.30±7.18 weeks; in the malignant group, the mean duration of the LAP was 7.05±5.38 weeks. A statistically significant difference was observed between the duration of lymph nodes and malignancy (p=0.016).

According to the lymph node level of LAP, malignancy rates were 25%, 33.3%, 25.9%, 50%, and 58.8% in level I, II, III, IV, and V, respectively. In our study, a significant difference was observed between the lymph node level and malignancy (p=0.029).

As shown in Table 2, multiple regression analysis was performed between gender, age, LAP size, duration of the disease, and location of LAP. The male gender was detected as the most influential risk factor in malignancy. As the results indicate, the male gender is associated with a 3.09 times higher risk than is the female gender, and neck level V is associated with a 2.6 times higher risk for malignancy than the other levels. Furthermore, increased age and duration of disease were significantly associated with malignancy. As the duration of the disease increases, the likelihood of LAP being malign decreases. No statistically significant effect of lymph node size was found.

DISCUSSION

Lymphadenopathies, which can be seen in both pediatric and adult populations, may be the first sign of many diseases. Although benign causes constitute the majority in etiology, causes related to malignancy also constitute a significant proportion. Therefore, enlarged lymph nodes disturb patients as well as physicians and it has to be taken into consideration. To determine the etiology of cervical LAP, the role of ENT examinations which include anamnesis and detailed endoscopic ex-

amination and imaging methods cannot be understated. However, it is not always possible to determine the specific cause of LAP in each patient; in such cases, a biopsy is performed. Excisional biopsy is considered the gold standard for diagnosis of LAP, [5, 6] and our clinic also uses excisional biopsy for clarification of LAP etiology. However, excisional biopsy has complications such as scar tissue and nerve damage. For these reasons, delineating the parameters associated with malignancy in the diagnosis of cervical LAP can help clinicians make a rapid and accurate diagnosis and can prevent potential complications from unnecessary surgeries. The aim of this study was to determine parameters that can help forecast cervical LAP diagnosis.

Some studies have investigated the characteristics of malignancy that can be useful for cervical LAP diagnosis. One such study of 95 patients revealed a significant relationship between malignancy and increased age [7], a finding echoed by Hetemoğlu and Erbek [8]. A study by Chau et al. [9] reported that male gender, increased age, White race, supraclavicular region, and lymph node size have a significant relationship with malignancy. In the same study, every 10-year increment in patient age increased the risk of malignancy by 1.64. Another study used multiple regression analysis to reveal that male gender, increased age, left-sided lesions, and lymph node size were associated with malignancy in patients younger than 18 years of age, male gender, and B symptoms in patients over 18 years of age. These authors also found that long-term and bilateral lymph nodes were associated with benign lesions [5]. Likewise, our results confirm that long-term lymph nodes are benign.

A study by Al Kadah et al. [10] found a significant relationship between malignancy and age, history of malignant disease, lymph node size, and ultrasonographic findings (absence of hilus, blurred outer contour, and decreasing Solbiati index values). The same study also reported that malignancy rates were higher in level IV and level V lymph nodes. Another study including 60 patients found that serum lactate dehydrogenase values, interleukin 2 receptor levels, age, and lymph node size were correlated to malignant LAP [11]. In studies restricted to pediatric populations, large lymph nodes, the presence of lymph nodes at multiple neck levels, and supraclavicular lymph nodes were found to be more strongly associated with malignant LAP [12, 13]. Cumulatively, these studies indicate that age, male gender, supraclavicular region, and lymph node size are reliable parameters for predicting malignancy in LAPs.

In this study, we investigated possible associations between both the gender and age of the patients and the side, size, duration, and level of the excised lymph node to identify parameters that can be helpful for predicting malignancy in persistent cervical LAPs. Although a statistically significant relationship was found between malignancy and male gender, age, duration of LAP, and lymph node level, no significant relationship was found between the side and size of the lymph node.

We note that the rate of the metastatic lymph node in malignancy patients in our study was only 14.2% for patients aged <40 years, which increased to 50% in patients aged >40 years. In light of these data, the most important reason for the increased age and malignancy risk is thought to be the increase in the number of metastatic lymph nodes, which corroborates the results of Al Kadah et al. [10]. We observed that malignancy rates in level IV and V lymph nodes were higher than those in level I, II, and III. Although the results did not reach statistical significance, lymph nodes ≥3 cm in size were observed to be more susceptible to malignancy. We further analyzed the data by performing multiple regression analysis, which revealed male gender as the most predictive risk factor for malignancy, followed by involved neck level, increased age, and duration of LAP. As the duration of the LAP increases, the lymph node is more likely to be benign. No statistically significant effect of the size of the lymph node was found.

Our study has a number of limitations due to its retrospective design, the first of which is that the imaging characteristics of lymph nodes, which can be used in the prediction of malignancy, were not included in this study since some of the patients were referred to our clinic after imaging methods were performed in an outpatient center. The second limitation is that the sample size of the study may limit the generalizability of the results. Further studies with larger patient populations could provide more comprehensive results.

Conclusion

Knowledge of the predictive factors for malignancy in persistent cervical LAPs is important to inform a quick and accurate diagnosis by clinicians. In our study, male gender was determined to be the most predictive risk factor for malignancy in patients with cervical LAP, followed by involved neck level, increased age, and duration of the disease. No significant association was found between the size or side of the lymph node and malignan-

cy. The results of this study suggest that early excisional biopsy should be considered for male patients with advanced ages if a new-onset LAP is detected, especially at neck level V.

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