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Analysis of Pathological Diagnoses in Cases with Axillary Lymphadenopathy: A Single Center Experience

Aksiller Lenfadenopatili Olgularda Patolojik Tanıların Analizi: Tek Merkez Deneyimi

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Açıklama/Disclosure: Yazarların hiçbiri, bu makalede bahsedilen herhangi bir ürün, aygıt veya ilaç ile ilgili maddi çıkar ilişkisine sahip değildir. Araştırma, herhangi bir dış organizasyon tarafından desteklenmedi. Yazarlar çalışmanın birincil verilerine tam erişim izni vermek ve derginin talep ettiği takdirde verileri incelemesine izin vermeyi kabul etmektedirler.

ÖZET

Amaç: Bu çalışmada, erişkinlerde aksiller lenfadenopati yapan benign ya da malign nedenlerin lenf nodu sayısı ve çapı, yaş, cinsiyet ve hastanın malignite öyküsü ile ilişkili olup olmadığını saptamayı amaçlıyoruz.
Gereç ve Yöntemler: Bu retrospektif çalışmaya hastanemize koltuk altında şişlik şikayeti ile başvuran ve patolojik lenf nodu saptanan 264 hasta dahil edildi. Olgular patolojik tanılarına göre kategorize edilerek belirtilen kriterler açısından karşılaştırıldı.
Bulgular: Tanılar 134 (%50,8) olguda benign, 130 (%49,2) olguda malign olarak saptandı. Lenf nodu çapı ile tanının benign veya malign olması arasında istatistiksel olarak anlamlı bir ilişki saptandı (p=0,004). Kadınlarda sırasıyla benign değişiklikler (%59,5), metastazlar (%24,5), lenfomalar (%16) görülürken erkeklerde lenfomalar (%47,5), benign değişiklikler (%36,6) ve metastazlar (%15,9) görüldü.
Sonuç: Aksiller lenfadenopatiler %50,8 benign durumlar, %27,9 lenfomalar, %21,3 metastazlar nedeniyle karşımıza çıkar. Malign nedenlere yaşlı erişkinlerde ve lenf nodu büyüdükçe daha sık rastlanır. Unutulmamalıdır ki malignite nedeniyle izlenen hastalarda aksiller lenfadenopatinin nedeni reaktif olabileceği gibi nüks veya ikinci bir malignite bulgusu da olabilir.

Anahtar Kelimeler: Aksilla, lenfadenopati, lenfoma, metastaz

ABSTRACT

Aim: In this study, we aimed to determine the causes of axillary lymphadenopathy in adults, and to determine whether benign or malignant causes are related to the number and diameter of lymph nodes, age, gender, and malignancy history of the patient.
Materials and Methods: This retrospective study included 264 patients who presented at our hospital with the complaint of underarm swelling and were determined with a pathological lymph node. The cases were categorised according to the pathological diagnoses, and compared with the specified criteria.
Results: The diagnoses were reported as benign in 134 (50.8%) cases and malignant in 130 (49.2%). A statistically significant correlation was determined between lymph node diameter and the diagnosis being benign or malignant (p=0.004). Benign changes (59.5%), metastases (24.5%), lymphomas (16%) were seen in females, respectively, while lymphomas were observed in males 47.5%, benign changes (36.6%) and metastases (15.9%).
Conclusion: Axillary lymphadenopathy occurs due to benign conditions in 50.8%, lymphomas in 27.9%, and metastases in 21.3%. Malignant causes become more prominent in older adults and as the lymph node grows in size. It must not be forgotten that just as the growth of axillary lymph nodes may be reactive in patients followed up because of malignancy, it may also be a sign of recurrence or second malignancy.

Key words: Axilla, lymphadenopathy, lymphoma, metastasis

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INTRODUCTION

Lymphadenopathy (LAP) is the general name given to the changes in number, size, and shape occurring in the lymph nodes for any reason. Lymphadenopathies may develop associated with benign causes such as infectious agents, reactive conditions, autoimmune connective tissue diseases etc. and also malignant causes such as metastatic diseases and lymphomas (1,2). In addition, some primary tumours may not be able to be determined with imaging methods and present with LAP. Sometimes the primary focus of tumours such as malignant melanoma and germ cell tumours is exhausted or regressed and they are determined with lymph node involvement (3). The majority of lymphadenopathies in children and young adults develop associated with viral or bacterial infections, and in adults the main cause of lymphadenopathy is malignant diseases (4).

The vast majority of published studies on this subject are related to whether or not a tumour is determined in the sentinel lymph nodes in patients with breast cancer. However, there are more different and complex causes in the differential diagnosis of non-sentinel axillary LAPs (5). There are few studies in literature that have examined the histopathological differential diagnosis of non-sentinel lymph nodes, and those studies have included low numbers of patients. The aim of this study was to be of help in using laboratory, radiological and pathological facilities in the most effective way to reach the diagnosis, by determining the causes that should first come to mind according to age and gender in patients presenting with axillary LAP. It was also aimed to determine what clues are given about the etiology by patient age, gender, and clinical history, and the size or number of excised lymph nodes.

MATERIALS AND METHODS

This retrospective study conducted in the Pathology Department of Antalya Training and Research Hospital included 264 patients of all ages who presented at the hospital in the last eight years with the complaint of underarm swelling and were determined with a pathological lymph node (>1 cm) following clinicoradiological examinations. The pathological lymph node was excised to investigate the etiology of axillary LAP in these patients. The patients included in the study were those with a known malignancy and those who developed axillary LAP during the follow-up period. Patients were excluded from the study if axillary lymph node dissection was performed at the same time as primary diagnosis, if mastectomy was performed because of breast carcinoma or dissection was applied to mastectomised axillary lymph node, or those with sentinel lymph node dissection.

The cases were categorised according to the pathological diagnoses, and investigations were made as to whether the age, gender, oncological history, and number and diameter of lymph nodes were associated with the diagnoses. When the diagnosis was malignant, the radiology reports were examined to determine whether or not tumour cells had spread to other lymph nodes or organs in the body.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS vn. 24 software (Statistical Package for Social Sciences version 24, IBM, Armonk, NY, USA). Patients with missing values in an outcome variable were excluded from any analysis on that variable. Descriptive statistics were expressed as mean, standard deviation (SD), minimum-maximum values, frequency, and percentile. Conformity of the data to normal distribution was assessed using the Kolmogorov-Smirnov test. As the data did not show normal distribution, non-parametric tests were applied to numerical variables. The Mann Whitney U-test, Kruskal Wallis test, and Chi Square tests were used to evaluate the relationships between parameters. Pearson correlation analysis was applied. A value of $p<0.05$ was considered statistically significant with a 95% confidence level.

RESULTS

Age and Gender

Evaluation was made of 264 patients comprising 163 (61.8%) females and 101 (38.2%) males, giving a female: male ratio of 1.6:1. The mean age of all the patients was 53.94±16.83 years, as mean 54.2±16.04 years in females, and mean 53.36±18.11 years in males. A statistically significant correlation was determined between gender and benign or malignant pathological diagnosis. Of the causes of lymphadenopathy, malignant diagnoses were determined at a higher rate in males.

Lymph node diameter, number, and spread

The diameter of the lymph nodes removed was found to be mean 2.96±1.60 cm (min. 1 cm, max. 15 cm). The diameter of the excised lymph nodes was determined to be mean 2.64±1.22 cm in cases with a benign diagnosis and 3.26±1.87 cm in cases with a malignant diagnosis. The diameter of axillary lymph nodes diagnosed as malignant in males was found to be statistically significantly larger ($p=0.013$). A statistically significant correlation was determined between lymph node diameter and benign or malignant diagnosis ($p=0.004$, $z=-2.865$). The lymph node diameter was found to be larger in cases with a malignant diagnosis than in those with a benign diagnosis (Table 1).

Oncological history

Of the total 264 cases, 194 (73.4%) had no history of known malignancy. Of the 70 patients with known malignancy, the previous diagnoses were breast carcinoma in 32 (11.7%), lymphoma in 19 (7.1%), malignant melanoma in 4 (1.5%), and other carcinomas in 15 (5.3%). The invasive

Table 1. Clinical features of axillary lymphadenopathies in cases

Gender		Localization			Number			Diameter(cm)
		Unilateral	Bilateral	Total	Single	Multiple	Total	
Female	Benign	69 (%71.1)	28 (%28.9)	97(%100)	39 (%40.2)	58 (%59.8)	97(%100)	2.66±1.28
	Malign	47(%71.2)	19(28.8)	66(%100)	15(%22.7)	51(%77.3)	66(%100)	2.90±1.27
Male	Benign	26(%68.4)	12(%31.6)	38(%100)	16(%42.1)	22(%57.9)	38(%100)	2.60±1.06
	Malign	27(%42.9)	36(%57.1)	63(%100)	12(%19)	51(%81)	63(%100)	3.64±2.29

carcinoma diagnoses of the 32 patients with previous breast carcinoma were invasive ductal carcinoma (n:22), invasive lobular carcinoma (n:7), medullar carcinoma (n:2), and apocrine carcinoma (n:1). The previous diagnoses of the 19 patients with lymphoma were Hodgkin lymphoma (n:7), diffuse large B-cell lymphoma (n:4), follicular lymphoma (n:3), chronic lymphocytic lymphoma (CLL) (n:3), marginal zone lymphoma (n:1), and Burkitt lymphoma (n:1). The primary tumours categorised as other carcinomas were GIS-origin carcinoma (n:4), squamous cell carcinoma (n:2), lung adenocarcinoma (n:2), infiltrative urothelial carcinoma (n:2), basal cell carcinoma (n:1), endometrium carcinoma (n:1), renal cell carcinoma (n:1), thyroid papillary carcinoma (n:1), and seminoma (n:1).

Pathological diagnoses

Of all the cases in the study, 134 (50.8%) were reported as benign (figure 1), and 130 (49.2%) as malignant (Table 2). Of the axillary lymph nodes diagnosed as malignant, lymphomas (figure 2) were determined in 56.9%, and metastases (figure 3) in %43.1. Pathological diagnoses by gender are shown in Table 3.

In female patients with no oncology history, reactive lymph node hyperplasia (44.7%), lymphoma (17%), malignant epithelial tumour metastasis (16.3%), non-necrotising granulomatous lymphadenitis (7.3%), necrotising granulomatous lymphadenitis (3.3%) were determined. In the female patients with an oncology history, the diagnoses were reactive lymph node hyperplasia (43.5%) malignant epithelial tumour metastasis (43.5%), lymphoma (10.9%) and non-necrotising granulomatous lymphadenitis (2.1%). In the male patients with no oncology history, the diagnoses were lymphoma (48.9%), reactive lymph node hyperplasia (26.3%), malignant epithelial tumour metastasis (7.5%), malignant melanoma metastasis (2.5%), rhabdomyosarcoma metastasis (2.5%), neuroendocrine carcinoma metastasis (1.3%) and other benign causes.

In the male patients with a known oncology history, the diagnoses were lymphoma (37.6%), reactive lymph node

Table 2. Histopathological diagnosis of excised axillary lymph nodes

Pathological diagnoses	Number of cases	Percent %
Benign		
Reactive lymph node hyperplasia	98	37.1
Non-necrotising granulomatous lymphadenitis	11	4.1
Necrotising granulomatous lymphadenitis	6	2.2
Tuberculous lymphadenitis	4	1.5
Sinus histiocytosis	5	1.8
Dermatopathic lymphadenopathy	4	1.5
Foreign body associated lymphadenitis	1	0.3
Cat scratch disease	1	0.3
Castleman's disease	2	0.7
AIDS-related lymphadenitis	1	0.3
Progressive transformation of germinal centers	1	0.3
Malign		
Metastatic carcinomas		
Breast carcinoma	37	14
Lung carcinoma	7	2.6
GIS-origin carcinoma	3	1.1
Squamous cell carcinoma	2	0.7
Renal cell carcinoma	1	0.3
Lymphoma		
Hodgkin lymphoma	19	7.1
Non-Hodgkin lymphoma	55	20.9
Metastatic malignant melanoma	4	1.5
Rhabdomyosarcoma metastases	2	0.7

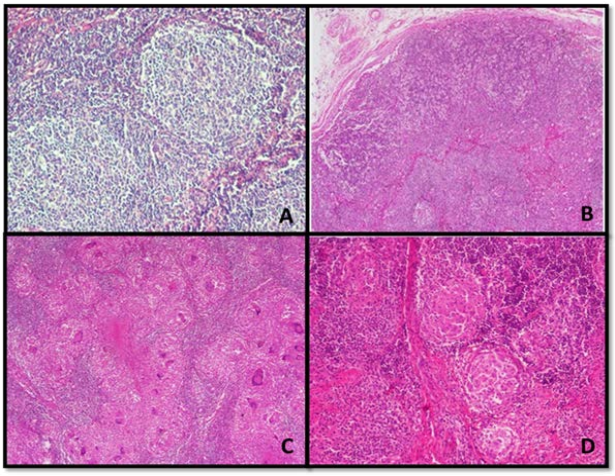

Figure 1. Benign diagnoses in axillary lymph nodes A. Reactive lymph node hyperplasia (H&E, x100) B. Dermatopathic lymphadenopathy (H&E, X40) C. Necrotising granulomatous lymphadenitis (H&E, x40) D. Non-necrotising granulomatous lymphadenitis (H&E, x100).

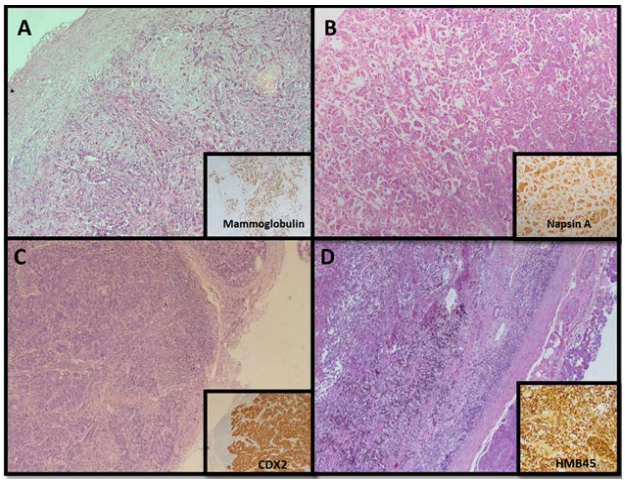

Figure 3. Cases with metastasis to axillary lymph nodes. A. Metastatic breast carcinoma, positive for Mammoglobulin. B. Metastatic lung adenocarcinoma, positive for Napsin A. C. Metastatic colon adenocarcinoma, positive for CDX2. D. Metastatic malignant melanoma, positive for HMB45. (Original magnification x40)

hyperplasia (33.3%), malignant epithelial tumour metastasis (12.5%), malignant melanoma metastasis (8.3%), non-necrotising granulomatous lymphadenitis (4.2%), and AIDS-related lymphadenitis (4.2%). Metastases determined in the screenings of patients after pathological diagnosis. In the screenings of the patients diagnosed with breast carcinoma metastasis following axillary lymph node excision, bone metastasis was determined in three, brain metastasis in two, lung metastasis in two, and widespread lymph node involvement in the whole body in one. In five of these eight patients, breast carcinoma was diagnosed for the first time due to the axillary lymph node excision.

Lung, brain, bone and liver metastases were detected in patients with malignant melanoma metastases. Brain, bone marrow, bones and surrenal gland metastases were determined in patients with lung carcinoma metastases. In the screenings of patients diagnosed with lymphoma, metastases were determined in the bone marrow, spleen, bone, lung and liver.

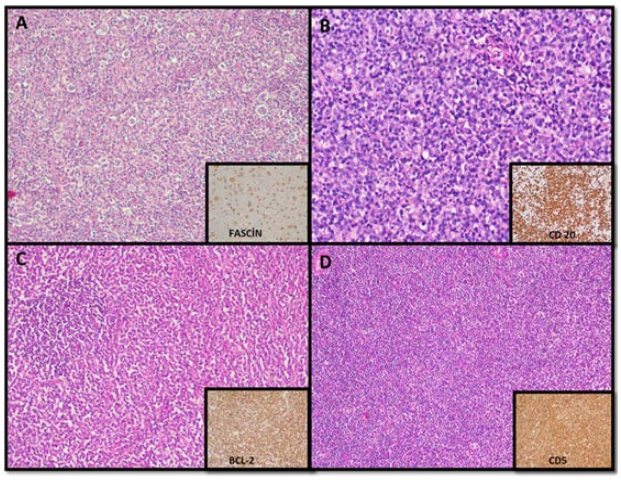

Figure 2. Cases diagnosed with lymphoma in the axillary lymph node. A. Hodgkin lymphoma (x200), positive for Fascin. B. Diffuse large B-cell lymphoma (x200), positive for CD20 C. Follicular lymphoma, Grade 3 (x100), positive for BCL2. D. Chronic lymphocytic lymphoma (x100), positive for CD5.

DISCUSSION

The vast majority of studies of lymphadenopathy etiology in Turkey have been conducted on the paediatric age group (6,7). In studies of adults, lymphadenopathies in other regions of the body have been included and the axillary region has been studied in lower numbers of samples (3,8). The current

Table 3. Distribution of benign and malignant pathological diagnoses by gender

Gender	Benign	Malign		Total
		Primer	Metastasis	
Female	97 (%59.5)	26(%16)	40(%24.5)	163(%100)
Male	37(%36.6)	48(%47.5)	16(%15.9)	101(%100)

study focussed on the causes of lymphadenopathy only in the axillary region with a large number of patients.

In a study by Gül et al.(8) investigating the causes of peripheral lymphadenopathy in adulthood, 67 cases were evaluated and axillary LAP was present in 36 patients. The pathological diagnoses were grouped in order of frequency as malignancies, caseified granulomatous lymphadenites, non-specific lymphadenites, and other causes. The distribution of malignancies was reported as Non-Hodgkin lymphoma (16.4%), Hodgkin lymphoma (10.4%), and metastases (7.5%). In another study which investigated the primary tumour focus of metastatis in lymph nodes, the tumours metastising to axillary lymph nodes in 6 patients who presented with LAP were found to be malignant melanoma, breast carcinoma, ovarian serous carcinoma, and papillary thyroid carcinoma, respectively (3). In the current study of 264 patients with axillary LAP, benign changes were determined in 50.8%, lymphomas in 27.9%, and metastases in 21.3%. A diagnosis was made of Non-Hodgkin lymphoma in 20.8% of the lymphomas and Hodgkin lymphoma in 7.1%.

There are very few studies in literature that have examined non-sentinel axillary lymph nodes (9,10). In a study by Schwab et al.,(9) 51 female patients were evaluated with no mass determined in the breast on USG or mammography, but with suspicion of lymph node in the axilla. Benign causes were determined in 33 of these patients and malignant causes in 18. Of the 33 patients determined with benign changes, these were determined to be non-specific inflammatory changes in 18, tuberculosis in four, HIV lymphadenopathy in two, and other causes in nine (SLE, cat scratch disease, chronic granulomatous lymphadenopathy).

In the current study, the benign changes observed in 134 (50.8%) of the 264 cases without gender differentiation were reactive lymphoid hyperplasia (37.1%), non-necrotising granulomatous lymphadenitis (4.1%), necrotising granulomatous lymphadenitis (2.2%), sinus histiocytosis (1.8%), tuberculosis lymphadenitis (1.5%), dermatopathic lymphadenopathy (1.5%), foreign body-related lymphadenitis (0.3%), Castleman disease (0.7%), cat-scratch disease (0.3%), AIDS-related lymphadenitis (0.3%), and germinal center transformation (0.3%).

In an extensive cohort study of 1165 non-sentinel axillary lymph nodes, Huang et al.(8) reported benign changes (41.2%), breast carcinoma (37.8%), lymphoma (16.7%), other carcinomas (2.4%), metastatic melanoma (1.5%), and sarcoma (0.4%) in females, and lymphoma (61.8%), benign changes (23.6%), metastatic melanoma (8.7%), other carcinomas (4.4%), breast carcinoma (0.9%), and sarcoma (0.6%) in males. Similarly in the current study, benign changes (n:97, 59.5%), metastases (n:40, 24.5%), and lymphoma (n:26, 16%) were observed in females, and lymphoma (n:48, 47.5%), benign changes (n:37, 36.6%) and metastases (n:16, 15.9%) in males.

In a study of 62 patients with no abnormal breast lesion, Ogawa et al.(5) reported malignant lymphadenopathy in two-thirds of the patients and benign changes in one-third. Bello et al.(11) studied 59 patients who presented with axillary mass and no history of breast cancer, and determined the causes of the axillary mass to be congenital in eight (13.6%) patients, reactive/infectious in 20 (34.6%), and neoplastic in 31 (52.5%). Of the 11 patients with non-Hodgkin lymphoma, seven were found to have diffuse large B-cell lymphoma, two lymphoblastic lymphoma, one small lymphocystic lymphoma, and one Burkitt lymphoma. Metastatic carcinoma was determined in five (16.1%) cases, and the primary focus of these was found to be the nasopharynx (n:2), the lungs (n:1), thyroid (n:1), and oesophagus (n:1). In the current study, of the 74 cases with a diagnosis of lymphoma, 19 were diagnosed with Hodgkin lymphoma and 55 with non-Hodgkin lymphoma. The distribution of the non-Hodgkin lymphoma diagnoses was follicular lymphoma (n:20), diffuse large B-cell lymphoma (n:15), small lymphocytic lymphoma (n:6), marginal zone lymphoma (n:4), anaplastic large cell lymphoma (n:4), mantle zone lymphoma (n:3), Burkitt lymphoma (n.2), and peripheral T-cell lymphoma (n:1). Metastasis was determined in 56 of the axillary lymph nodes in the current study. Of these cases, the primary focus in 50 (18.9%) of the metastatic carcinomas was the breast (n:37, 14%), lungs (n:7, 2.6%), GIS (n:3, 1.1%), skin (n:2, 0.7%) and kidney (n:1, 0.3%). The other six cases of metastasis were metastasis of malignant melanoma in four cases and of rhabdomyosarcoma in two.

It must not be forgotten that just as the growth of axillary lymph nodes may be reactive in patients followed up because of malignancy, it may also be a sign of recurrence or second malignancy. For example in a case in the current study with a history of signet ring cell carcinoma in the stomach, breast carcinoma metastasis was determined in the axillary lymph node. In another of the current study cases with a history of infiltrative urothelial carcinoma in the bladder, the axillary lymph node diagnosis was reported as follicular lymphoma. Of the 32 patients with previously known breast carcinoma, breast carcinoma metastasis was observed in 17 (53.1%), reactive lymphoid hyperplasia in 12 (37.5%), SLL in 2 (6.3%), and marginal zone lymphoma in 1 (3.1%). Of the 19 patients with previously known lymphoma, reactive lymph node hyperplasia was determined in 7 (36.8%), non-necrotising granulomatous lymphadenitis in 1 (5.3%), AIDS-related lymphadenitis in 1 (5.3%), Hodgkin lymphoma in 6 (31.6%), CLL in 2 (10.5%), diffuse large B-cell lymphoma in 1 (5.3%), and follicular lymphoma in 1 (5.3%).

The axillary lymph node dissections or sentinel lymph node excisions were not performed in this study because of

breast carcinoma, but to evaluate patients who presented with the complaint of under-arm swelling and were determined with pathological lymphadenopathy. This is the first study in literature to present the pathological diagnoses of axillary LAP together with age, gender, oncological history, diagnosis and distribution of the lymph nodes, and the results of patient body scanning after the diagnosis.

In conclusion, the results of this study demonstrated that malignant causes become more prominent in older adults and as the lymph node grows in size. Metastases were observed to be the most common malignant causes in females, and lymphomas in males. Sometimes the presence of malignancy is first signalled with the excision of the pathological axillary lymph node. In these patients, screening should be performed rapidly and treatment should be started. In the approach to patients, knowing previously diagnosed malignancies will help in the effective use of histopathological and immunohistochemical methods at the diagnosis stage and thus a result can be reached in a short time. However, it must be kept in mind that secondary malignancies can develop in these patients.

Etik Kurul: This study was reviewed and approved by the ethics committee of Antalya Training and Research Hospital (Approval number: 11/ 16, Date: 23/07/2020).

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