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A Clinicopathological Evaluation of the Patients with Supraclavicular Lymphadenopathy: A Retrospective Analysis

ABSTRACT

Objective: The accuracy of biopsy technique and pathological reports from supraclavicular lymphadenopathy (ScLAP) biopsies in adults were evaluated.

Methods: Five hundred sixty-four lymph node excisions or aspiration biopsies because of lymphadenopathy from all cervical regions were retrospectively assessed. Demographic and clinical data collected included gender, age, preoperative diagnosis, biopsy or cytology type, location of ScLAP, and biopsy diagnosis.

Results: After exclusions for a variety of clinical and diagnostic reasons, the final analysis included 156 patients, of whom 34 (21.8%) underwent fine-needle aspiration (FNA), 69 (44.2%) core needle biopsy (CNB), and 53 (34%) excisional biopsies. In this study, 52 (33.3%) benign and 93 (59.6%) malignant diagnoses were reported. Totally, 11 of the 34 (32.3%) FNAs were insufficient for diagnosis. The size of the ScLAP (<10, 11-20, 21-30, >30 mm) did not affect malignancy risk. Patients aged > 55 years had a significantly greater likelihood of malignancy than younger patients. Logistic regression analysis showed that malignancy risk assessed by odds ratio (OR) was increased by male gender (P = .004; OR = 1.428; 95% CI 1.106-1.842), left side (P = .003; OR = 1.502; 95% CI 1.125-2.005) and age > 55 years (P = .007; OR = 2.631; 95%CI 1.275-5.431).

Conclusion: Regardless of size, biopsy or cytology should be performed in all appropriate masses. Although the size of the lymph node had no effect on malignancy risk, male gender, older age, and left side were associated with a significant increase in the likelihood of malignancy.

Keywords: Clinicopathology, correlation, malignancy, supraclavicular lymphadenopathy, biopsy

INTRODUCTION

For patients presenting with a mass in the neck, a rapid diagnosis is essential in deciding future treatment and management.[1,2] Difficulties are often experienced for differential diagnoses of lesions in the neck region in any age group, as this region exhibits vital organ diversity and delicate neurovascular networks.[1-3]

Neck lymphadenopathy can be the first sign of head and neck cancers and neoplasm in distant organs, such as lungs, breast, gastrointestinal system, pancreas, and prostate. Additionally, malignant melanoma and sarcomas also may be observed in the neck region as metastatic tumors.[3-6]

Cell block cytology is the technique used for the evaluation of liquids collected via fine-needle aspiration (FNA). It can be more useful in certain cytopathological diagnoses and tumor categorization.[7] Following a core needle or excisional biopsy, comprehensive histopathological and immunohistochemical (IHC) examination are critical in the diagnosis and treatment of the patient.[5]

Depending on where the primary tumor is located, the location of metastatic lymph nodes also changes. Supraclavicular lymph nodes (ScLN) have drainage from both the upper and lower parts of the body. All head and neck regions, thoracic and abdominal, and even inguinal lymphatics can drain into this area. Supraclavicular lymphadenopathies (ScLAP) are present in approximately 50% of malignancies, such as the lung, thyroid, breast, gastrointestinal tract, and urogenital system cancer.[6]

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This retrospective study investigated the diagnostic accuracy and yield of different ScLN biopsy types to evaluate malignancy rates in ScLAP among patients treated in a single tertiary center.

METHODS

Patients

This was a retrospective evaluation of FNA, excisional, or core needle biopsy (CNB) data from patients with cervical lymph nodes, diagnosed in a tertiary center, between January 2017 and December 2019. The inclusion criteria were: supraclavicular lymphadenopathy (ScLAP), FNA, CNB or excisional biopsy, and age over 18 years. The lymphadenopathies included in the study were located below the horizontal axis of the cricoid cartilage's lower border, above the clavicle, lateral and posterior to the sternocleidomastoid (SCM) muscle, medial and anterior to the trapezius muscle's anterior border. The exclusion criteria were: patients with cervical lymph node biopsies other than ScLN and those younger than 18 years old. All cases were diagnosed with ScLAP and evaluated by age, gender, ScLAP location, ScLAP size, biopsy method, and postoperative pathology. Malignancy risk was compared according to age (18-40 vs. >40, 18-50 vs. >50, 18-55 vs. >55, 18-60 vs. >60 years of age). ScLAP sizes given in the study were radiologically measured through the short axis of the lymphadenopathy. All procedures involving human participants were in accordance with the principles of the Declaration of Helsinki. The study was approved by the Kocaeli University Ethical Committee of Non-invasive Clinical Research (GOKAEK-2020/3.04 2020/32). Written informed consent was obtained from all participants before FNA, CNB, or excisional procedures.

Surgical Procedures

The choice of procedure was first decided by a clinician. If apparent symptoms were weight loss, night sweating, loss of appetite, an excisional biopsy was the first choice. Patients who were radiologically highly suspicious for ScLAP but without clinical symptoms were referred to an interventional radiologist who decided whether to perform FNA or CNB. FNA was mostly chosen for inaccessible lesions. CNB was chosen for the rest of the lesions.

Excisional biopsies were performed under local anesthesia. Palpable ScLAPs were excised directly but suspicious, non-palpable lymph nodes were marked with guide wires using ultrasonography by an interventional radiologist on the day of surgery.

MAIN POINTS

- ScLAP has high risk for malignancy in adults.
- Left sidedness, male gender, and age over 55 years are increasing risk factors for malignancy. Expeditious evaluation of these patients should be performed.
- FNA can be useful for distinguishing malign from benign conditions but can be non-diagnostic causing delay in treatment.
- Regardless of size, biopsy or cytology should be performed in all suspicious masses.

Patients were placed in the supine position for biopsy. After cleaning and draping the area, a 3-5 cm horizontal incision was performed. For the left supraclavicular region, care was taken not to injure the ductus thoracicus.

A radiologist performed ultrasound-guided lymph node CNB/FNAB using a Toshiba Aplio XG (Toshiba Medical Systems, Tokyo, Japan) machine for sonographic evaluation. For FNA, a 25G needle attached to a 10 mL syringe was used. For CNB, after injecting approximately 10 ccs of lidocaine-1% for local anesthesia, core biopsy was performed with a 16G needle using a Bard Magnum biopsy device (Covington, USA). The device was set at 22 mm (long) and 15 mm (short) throw, depending upon the size of the node size and proximity of the vessels. The number of entries into the mass depended on the size of the mass and the amount of material taken from each entry. Rapid on-site evaluation (ROSE) could not be performed due to a shortage of specialist physicians in the pathology department.

Histopathology

Air-dried smear slides were stained with May–Grünwald Giemsa stain. Alcohol-fixed slides were stained with Papanicolaou stain. Due to occasional technical problems with our cell block technique, the radiologist prepared multiple cytological smears from the entire aspirate without preparing a cell block.

All lymph node tissues were fixed in 10% neutral formaldehyde. Resected tissue was cut into 3 mm thick slices to identify lymph nodes. Tissues were then embedded in paraffin, cut into 5 μm sections, and stained with hematoxylin and eosin (H&E).

All examinations were performed under light microscopy by histopathologists. Reactive benign processes, such as granulomatous inflammation, were directly reported. If required, an additional examination was performed.

Immunohistochemistry

IHC examinations were performed on 4 mm thick formalin-fixed, paraffin-embedded sections, mounted on charged slides, to diagnose carcinoma metastases, melanoma or lymphoma, according to neoplasm type as indicated in the differential diagnosis. Relevant staining was performed on representative sections and in samples that were morphologically suspicious for a differential diagnosis. Finally, samples were reported as "metastatic lymphadenopathy" or "primary lymphoproliferative disease," according to IHC findings.

Statistical Analyses

All statistical analyses were performed using SPSS for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to assess the normality of data distribution. Continuous variables were expressed as medians and interquartile range (25th-75th percentiles), and categorical variables were expressed as numbers (percentages). Categorical variables were compared with the chi-square test. A $P < .05$ was considered statistically significant. To determine malignancy risk factors, logistic regression risk analysis was performed.

RESULTS

Initially, 564 head and neck FNA, CNB, and open biopsies performed between 2017 and 2019 were identified. Of these, 405

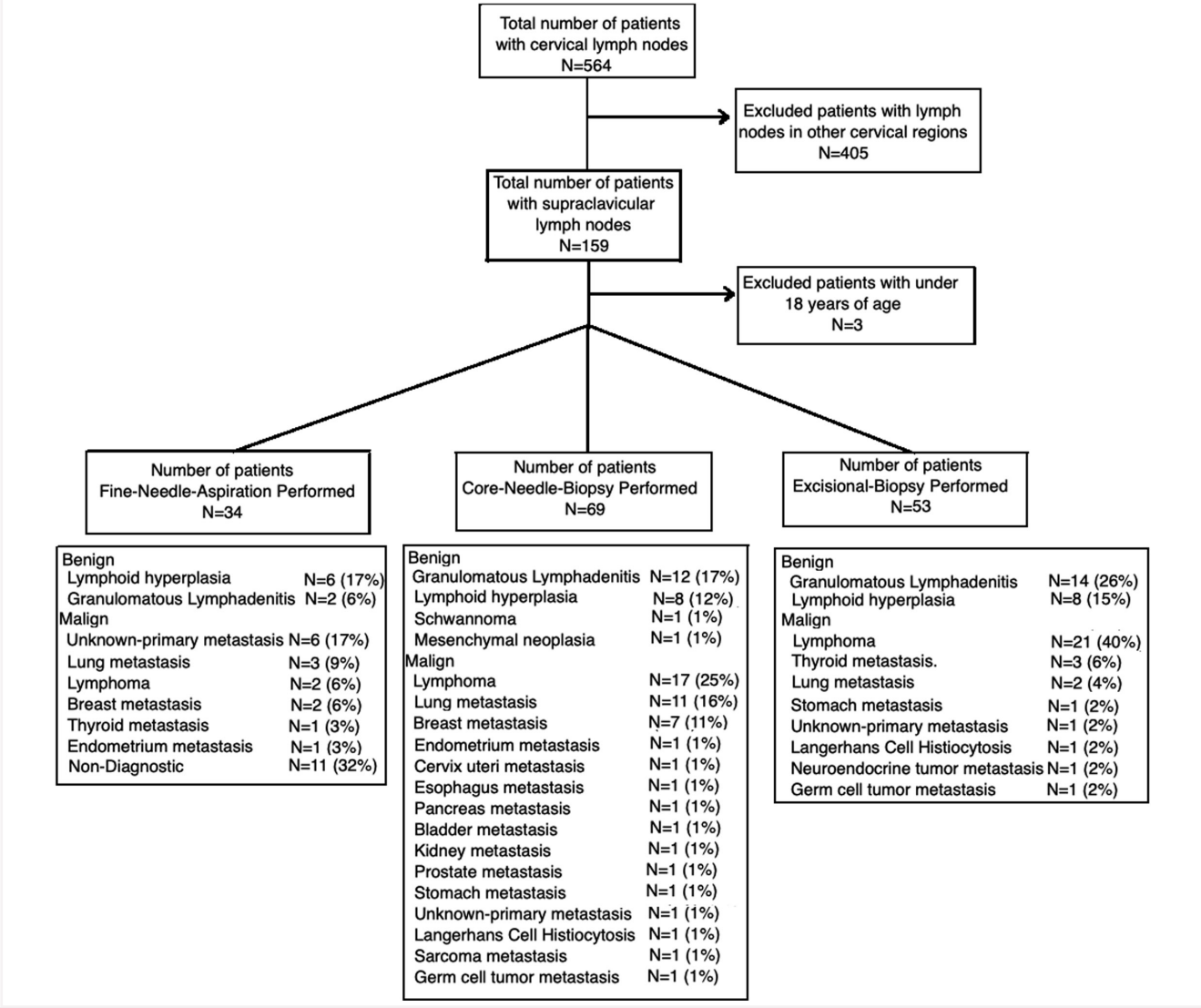

Figure 1. Distribution of cases with supraclavicular lymphadenopathy.

biopsies from other cervical regions, and 3 patients with ScLAP biopsies < 18 years of age were excluded. This resulted in 156 patients who had undergone ScLAP biopsy and/or cytology examination, and these were included in the analysis (Figure 1).

There was a total of 34 (21.8%) FNA. Of these 8 (23.5%) were benign and diagnoses included reactive lymphoid hyperplasia ($n=6$) and granulomatous lymphadenitis ($n=2$). A further 15 (44.1%) were malignant and diagnoses included unknown primary ($n=6$), lung ($n=3$), lymphoma ($n=2$), breast ($n=2$), thyroid ($n=1$) and endometrium ($n=1$). Of note, 11 (32.35%) of FNAs were non-diagnostic.

Sixty-nine (44.2%) CNBs were performed. Of these 22 (31.9%) were benign and diagnoses included granulomatous lymphadenitis ($n=12$), reactive lymphoid hyperplasia ($n=8$), schwannoma ($n=1$) and mesenchymal neoplasia ($n=1$). A further 47 (68.1%) were malignant and included 27 (57.45%) carcinoma metastases comprising mainly lung ($n=11$) and breast ($n=7$) with one each of endometrium, cervix uteri, esophagus, pancreas, bladder, kidney, prostate, stomach, and unknown primary. Other identified malignancies included 17 (36.2%) lymphomas, one (2.1%) Langerhans cell histiocytosis, one sarcoma metastasis, and one (2.1%) germ cell tumor metastasis.

In addition, 53 (34%) excisional biopsies were evaluated. Twenty-two (41.5%) were benign and diagnoses included granulomatous lymphadenitis ($n=14$) and reactive lymphoid hypertrophy ($n=8$). A further 31 (58.5%) were malignant and included lymphoma ($n=21$), carcinoma metastases ($n=7$; thyroid $n=3$, lung $n=2$, stomach $n=1$, and unknown primary $n=1$), with 1 each of germ cell tumor metastasis, neuroendocrine tumor and Langerhans cell histiocytosis.

The median (IQR) age was 52.0 (37.25-64.75) years with 47 (30.1%) patients aged < 40 years and the remaining 109 (69.9%) older.

Table 1. Comparison of Risk Factors for Malignancies

Factor	Group	Benign	Malign	Total ($n=145$)	*P*
Age (Years)	≤40	14 (31.8%)	30 (68.2.%)	44 (100%)	.501
	>40	38 (37.6%)	63 (62.4%)	101 (100%)	
	≤50	28 (43.1%)	37 (56.9%)	65 (100%)	.119
	8 > 50	24 (30.0%)	56 (70.0%)	80 (100%)	
	≤55	37 (45.1%)	45 (54.9%)	82 (100%)	**.007**
	>55	15 (23.8%)	48 (76.2%)	65 (100%)	
Gender	Male	18 (24.7%)	55 (75.3%)	73 (100%)	**.004**
	Female	34 (47.2%)	38 (52.8%)	72 (100%)	
Side	Left	23 (27.1%)	62 (72.9%)	85 (100%)	**.003**
	Right	31 (51.7%)	29 (48.3%)	60 (100%)	
Surgical Procedure	FNA	8 (34.8%)	15 (65.2%)	23(100%)	.49
	Core needle biopsy	22 (31.9%)	47 (68.1%)	69 (100%)	
	Excisional Biopsy	22 (41.5%)	31 (58.5%)	53 (100%)	
LAP Size	≤10 mm	9 (52.9%)	8 (47.1%)	17 (100%)	.493
	11-20 mm	22 (32.8)	45 (67.2%)	67 (100%)	
	21-30 mm	13 (35.1%)	24 (64.9%)	37 (100%)	
	>30 mm	8 (33.3%)	16 (66.7%)	24 (100%)	
Total		52 (35.9%)	93 (64.1%)	145 (100%)	

Data of 11 insufficient cytologies and biopsies are not shown in table. LAP, Lymphadenopathy

Seventy-six (48.7%) were male, and 80 (51.3%) were female. Ninety-three biopsies and cytologies (58.7%) were malignant, and two-thirds ($n=63$, 67.7%) of the patients with malignant results were older than 40 years. There was no increased risk for age subgroup being older than 40 years ($P = .501$; odds ratio (OR)=1.093; 95% CI 0.849-1.407). Similarly, there were 56/80 (70%) malignancies in patients older than 50 years but again there was no increased risk for this age subgroup ($P = .119$; OR=1.436; 95% CI 0.928-2.221). However, a significant association between age > 55 years and the likelihood of having a malignant ScLN biopsy result was identified. In this age group 48/63 (76.2%) biopsies were reported as malignant ($P = .007$; OR=2.631; 95% CI 1.275-5.431) (Table 1).

Patients were also compared by gender for malignancy risk. In the study, 55 (75.3%) of 73 male patients had malignant biopsies versus 38 (52.7%) of 72 female patients. On logistic regression analysis, the gender difference was found to be significant with male patients having a higher risk of malignancy ($P = .004$; OR=1.428; 95% CI 1.106-1.842).

Left-sided biopsies were performed in 85 patients (58.6%), and right biopsies in 60 patients (41.4%). Sixty-two (73.9%) of the left-sided, and 29 (48.3%) of the right-sided biopsies were malignant. Left-sided ScLAP was associated with a statistically significant risk for malignancy ($P = .003$; OR=1.502; 95 % CI 1.125-2.005) (Table 1).

Interestingly, the size of mass (<10 mm vs. 11-20 mm vs. 21-30 mm vs. >30 mm in diameter; $P = .493$) did not affect malignancy risk. The rate of malignancy for lesions < 10 mm was 52.9%, for 11-20 mm 32.8%, for 21-30 mm 35.1%, for > 30 mm 33.3%. Malignancy rates and *P* values according to ScLAP size are shown in Table 1.

Entirely 31 (58.4%) of 53 excisional biopsies, 47 (68.1%) of 69 core needle biopsies and 15 (65.2%) of 23 FNA cytologies were malignant. The malignancy risk for the different sampling methods did not significantly differ ($P = .545$). Patient age, gender, location, operation procedure, and malignancy distribution are shown in Table 1.

The most frequent complaint was neck mass, observed in 102 (65.3%) patients. Fourteen (9%) had no local or systemic symptoms but were followed up for other conditions. The remaining symptoms were loss of weight in 34 patients (21.8%), loss of appetite in 34 (21.8%), fever in 32 (20.5%), fatigue in 25 (16%), and dyspnea in 17 (10.9%).

Among the 52 benign lesions, granulomatous lymphadenopathy was the most common diagnosis, detected in 28 biopsies (17.9%) and reactive lymphadenopathy in 22 patients (14.1%). The most severe malignant diagnoses included 40 (25.6%) lymphomas, 16 lung metastases (10.2%), 9 breast metastases (5.8%), and 4 thyroid metastases (2.6%) (see Figure 1). Some examples of diagnostic histopathologic and the IHC findings from patients included in this study are given in Figures 2-5.

DISCUSSION

Clinical intervention for neck mass is a challenging issue for both patient and clinician. Pynnonen et al.[1] recommended that masses in the neck area, >1.5 cm in size, and present for more than 2 weeks had an increased malignancy risk and should undergo FNA.[1] FNA may be useful for diagnosis, but its inability to ascertain a definitive diagnosis in some cases may cause diagnostic delay.[8] This delay depends on the availability of health care resources and the patient's availability for repeat biopsy. Non-diagnostic FNA in ScLAP has been reported to

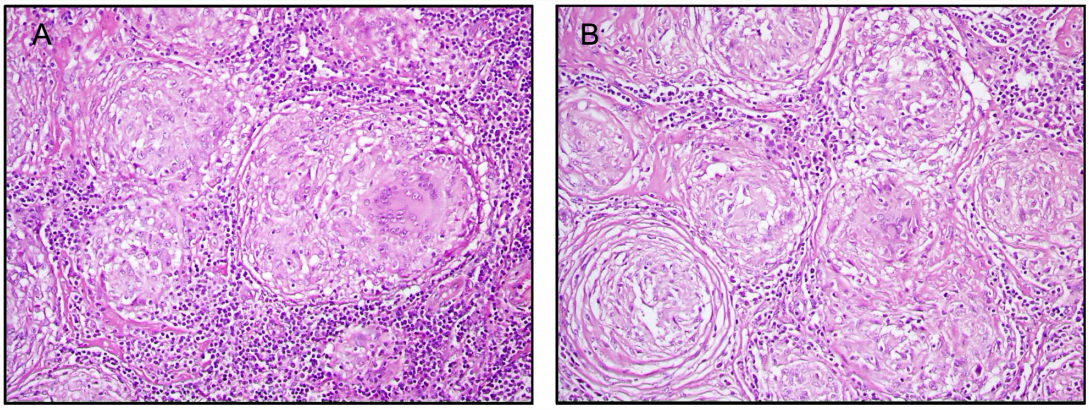

Figure 2.a,b. (A & B) Granulomas, showing lymph node structure, including giant cells without necrosis (hematoxylin and eosin staining, 200× magnification).

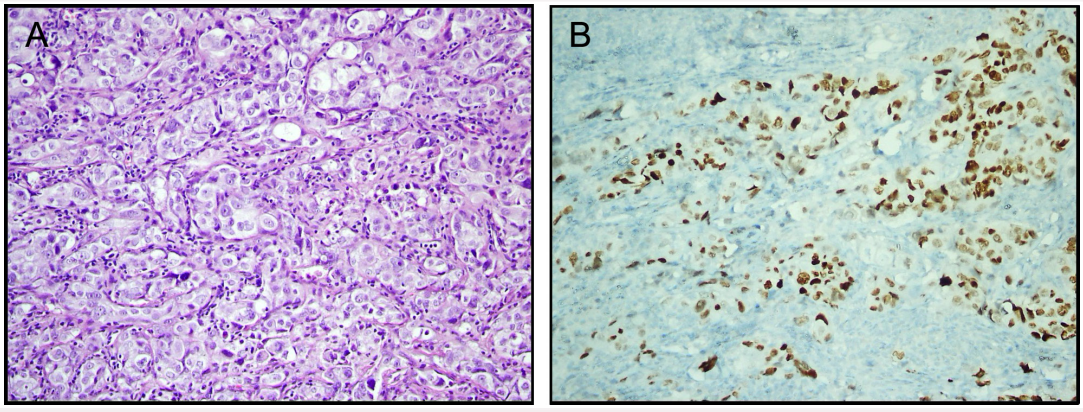

Figure 3.a,b. (A) Atypical epithelial cells showing the lymph node structure (hematoxylin and eosin staining, 200× magnification). (B) TTF-1-positive cells from 3A, TTF-1, 200×.

range between 18 and 21%.[9,10] The rate of non-diagnostic FNA in our study was approaching a third. The higher rate in our study was probably associated with the lack of ROSE due to a shortage of specialist histopathologists.

When aspiration biopsy findings are non-diagnostic, an open biopsy or core biopsy should be considered. Gupta et al.[10] evaluated 218 FNA cases and found 41 unsatisfactory results in ScLAP patients. Open biopsies of these cases showed malignancy in

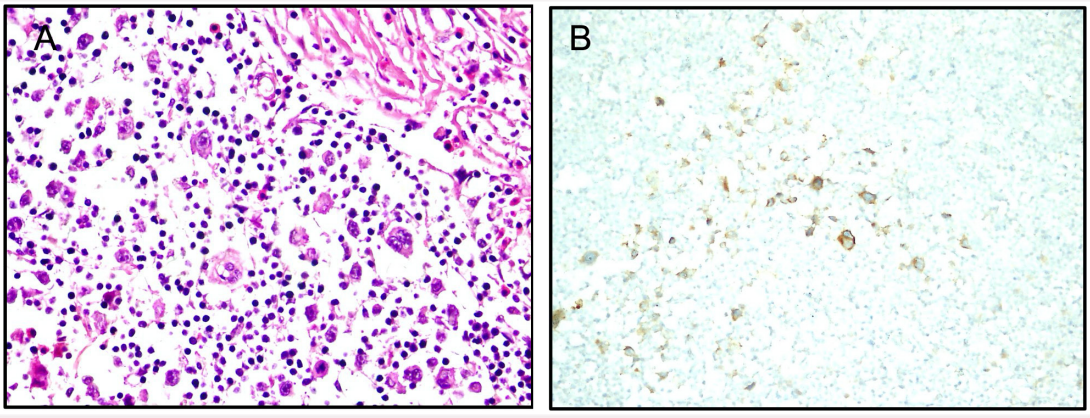

Figure 4.a,b. (A) Reed Sternberg cells in a Hodgkin lymphoma case (hematoxylin and eosin staining, 400× magnification). (B) CD30-positive cells from 4A, (CD30 stained at 200× magnification).

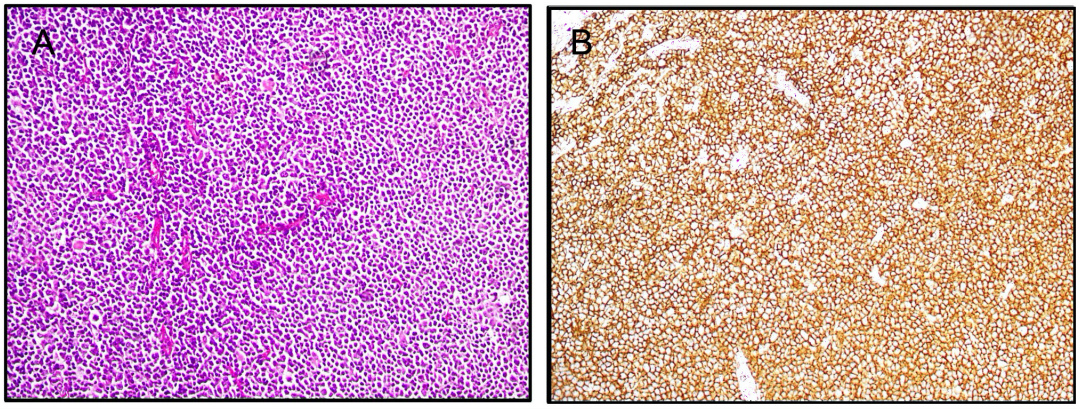

Figure 5.a,b. (A) Small round mature lymphocytes in a small lymphocytic lymphoma case (hematoxylin and eosin staining, 200× magnification). (B) CD20-positive cells from 5A (CD20 stained, 200× magnification).

5 patients (12%). In the present study, there were 11/34 (32.3%) insufficient FNAs. Unfortunately, none of these patients underwent a second biopsy at our center. However, we were able to ascertain the second biopsy results in 6 (54%) who underwent CNB. These 6 final diagnoses included: granulomatous lymphadenitis ($n=2$), mesenchymal neoplasia ($n=2$), reactive lymphoid hyperplasia ($n=1$); and 1 patient was diagnosed with lymphoma. In these 6, the proportion (16.7%) who had a malignant result was similar to that reported by Gupta et al[10]

The left supraclavicular region has a high risk of malignancy because of the thoracic duct drainage.[2] Nasuti et al[11] reported malignancy in 77 of 106 (73%) ScLAP examinations, and reported that malignancy rates in both right and left ScLN did not differ significantly.But he also noticed that infradiaphragmatic tumors are more likely to metastasize left ScLN. However, there was a significantly higher rate of malignancy in left-sided biopsies compared to right-sided in our cohort with a 1.5-fold increased OR including both infradiaphragmatic and supradiaphragmatic tumors. Therefore, the left ScLAP may require an earlier assessment than the right.

Pyonnen et al[1] suggested a cut-off of 1.5 cm lymph node diameter for FNA aspiration but in our cohort, in lymph nodes ≤10 mm in diameter, there was a 47.1% malignancy rate. Six were carcinoma metastases from lung, breast, or unknown primary, and two lymphomas. The rate of malignancy for 11-20 mm, 21-30 mm, >30 mm ScLAPs were 67.2%, 64.9%, 66.7%, respectively. Our results indicate that size of a node does not correlate well with malignancy risk, and it is advisable to evaluate each case with all available diagnostic tests including radiological imaging. We suggest performing a biopsy regardless of ScLN size if the lymph node is accessible via ultrasound guidance.

The thoracic duct drains from the pelvis to the thorax[3] and conveys around 75% of all lymph fluid back to the venous circulation, suggesting pulmonary, gastric, or testicular malignancies could develop metastases in this area. Chen et al.[12] reported lung, breast, liver, and prostate carcinomas from supraclavicular core-biopsies and diagnosed colonic carcinoma from excisional biopsies. In our study, all pulmonary, breast, and testicular metastases were detected in biopsies taken from the supraclavicular region. Lung cancer in the upper lobes can directly metastasize into the thoracic duct, resulting in a stage IV tumor, leading to a poor prognosis. [13] Breast metastasis to the ScLN is also associated with a poor prognosis; 7% of patients with breast cancer have a supraclavicular metastasis.[14] Van Gledder et al[15] highlighted that germ cell tumors may metastasize in 4% of patients.They suggested performing a neck dissection for cervical metastasis in patients with advanced-stage disease.

Benign neck lymph nodes may be due to infection and can lead to benign tumors.[2,4] Neck masses persisting for several months may be clinically confusing in terms of malignancy. However, in some cases, atypical mycobacteria, cat scratch disease, or granulomatous infections should be considered in the differential diagnoses.[2,4,6,16] In this study, the most common benign lesion in patients with ScLAP was granulomatous lymphadenopathy. Popescu et al. assessed mycobacterial lesions in patients' lymph nodes, and observed that well-differentiated granulomas were the most frequently diagnosed mass. The ScLN was the third most common location for mycobacterial lesions in lymph nodes of the head and neck.[17] Saifullah et al.[18]showed a 39.3% granulomatous infection frequency in their study of supraclavicular lymphadenopathies.

Özkan et al[7] reported non-significant differences in malignancy risks between the genders.[7]However, previous studies have reported that being male conveys a greater malignancy risk when undergoing ScLN biopsy, as reported in our study.[5,19] Males are also less likely to promptly visit a physician or to disregard symptoms.[6] Therefore, male patients with ScLAP should be investigated thoroughly for malignancy.

Being older than 40 years was indicated as a risk factor for neck masses which were associated with increased risk of head and neck malignancies.[1] However, in our study, there was no significant difference between patients aged ≤ 40 or > 40 years. No significant risk of malignancy with age was identified in our cohort until the age of > 55 years (P = .007). No patients in our cohort were identified with head and neck primary tumors, which may explain the lack of age associated with the over 40-year-old group. The cancers which were most likely to metastasize and present as ScLAP in our study were lung and

breast cancers. It has been reported that the median age of diagnosis is 61 years for breast cancer and 70 years for lung cancer, which may explain the finding of age association in our cohort.[20]

CONCLUSION

Left-sided ScLAP and male gender were found to be associated with an increased risk of malignancy in patients undergoing ScLN biopsy in our cohort. Expeditious evaluation of these patients should be performed. Regardless of lymph node size, biopsy, or cytology should be performed in all suspicious masses, using ultrasound guidance if necessary. FNA can be useful for distinguishing malign from benign conditions but can be non-diagnostic causing delay in treatment.

Ethics Committee Approval: Ethics committee approval was received from the Ethics Committee of Kocaeli University (KOU-GOKAEK-2020/32).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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