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Original Article

Where do these guests come from? A diagnostic approach for metastatic lymph nodes

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ABSTRACT

Objective: In cases presenting with lymphadenopathies (LAP) without a primary focus detected by simple radiological methods, the primary tumor can be diagnosed by a histopathological evaluation of the metastatic lymph nodes. We aimed to discuss the nonhematological malignancies presenting with lymphadenopathies and the histopathological results for primary tumors.

Material and Methods: In this retrospective study, cases diagnosed with metastasis in excisional lymph nodes between January 2013 and June 2016 were assessed for a histopathological diagnostic approach

Results: Among 632 lymph node biopsies, a total of 21 cases, involving 12 male and 9 female patients with a mean age of 57.23 y (range, 33–92 y), of nonhematological solid tumors were included. The most common localizations of the involved lymph nodes were inguinal (n=8), axillary (n=6), cervical (n=4), and supraclavicular (n=3) region. The most common primary tumors were malignant melanoma (n=6), breast carcinoma (n=4), ovarian carcinoma (n=2), squamous cell carcinoma (n=2), and germ cell tumor (n=2). Others were papillary thyroid carcinoma, renal cell carcinoma, urothelial carcinoma, prostate adenocarcinoma, and endometrial adenocarcinoma.

Conclusion: Nonhematological malignancies presenting with lymphadenopathies are one of the most complicated cases for clinicians. The histopathological evaluation of the excisional metastatic lymph node biopsies is an important method because of cost effectiveness and easy applicability.

Keyword: Immunohistochemistry, lymph node metastasis, unknown primary tumor

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INTRODUCTION

Lymph node metastasis is the most common mode for the spread of carcinomas and solid tumors, such as malignant melanoma (1). Although many radiological and scintigraphy methods were being used for the diagnosis of solid tumors, an excisional biopsy of metastatic lymph nodes can still be necessary especially for oncological treatment procedures (2). In addition, some of the primary tumors presented with lymphadenopathies (LAP) could not be located by imaging. Moreover, the primary foci of malignant melanoma and germ cell tumors can be burnout tumors, which can only be diagnosed by an excisional biopsy of the involved lymph nodes.

Metastatic lymph nodes usually present as palpable masses but can be found by physical examination or imaging studies of patients by investigating for various symptoms (2). In asymptomatic cases, palpable LAP is generally very striking for both clinicians and patients and allows systemic evaluations. However, an excisional biopsy of these enlarged lymph nodes can also be a diagnostic approach for uncertain imaging results.

In this study, we aimed to assess the nonhematological malignancies presenting with LAP and reveal the histopathological approach for the diagnosis of the primary focus.

MATERIAL AND METHODS

All lymph node excisional biopsies (n=632) performed between January 2013 and June 2016 were assessed retrospectively. Every case was investigated for the diagnosis of a known primary focus from hospital records and medical history. Patients with known solid primaries and lymph node metastases diagnosed synchronously with the primary tumor (n=144) were excluded. Cases presenting with lymph node enlargement and diagnosed as any form of hematological malignancies (n=109) or any form of reactive hyperplasia (n=310) and specific infections (n=48) were also excluded. The demographic features and localizations of the lymph nodes were obtained from pathology reports.

Cases with palpable masses were examined by the applied clinicians, and first-step radiologic tests, such as X-ray, ultrasonography (USG), and mammography, were performed; in cases where no explanatory result was found for lymph node enlargement, an excisional biopsy was offered to the patients.

The indications of lymph node excision determined by the clinicians were as follows:

- Primary tumor not assessed using physical examination and first-step imaging studies (X-ray, USG, or mammography)
- Negative biopsies from possible primaries
- Suspicious cases for hematological or nonhematological malignancies

None of the patients underwent positron emission tomography/computerized tomography (PET/CT) before the excision of the enlarged lymph nodes.

Cases diagnosed as reactive LAP or hematological malignancies in addition to patients treated at another center or unavailable for follow up were excluded. Written informed consent was obtained from patients before the operation who participated in this study.

The hematoxylin–eosin stained slides of excisional biopsies were examined in addition to the slides analyzed by immunohistochemistry (IHC). All cases were immunohistochemically analyzed using the (Leica Bond Max®, Leica Biosystems, Germany) automated staining procedure. Antibodies used for IHC analysis was chosen systematically according to the morphological appearance of the entities encountered in the pathological differential diagnosis. The final diagnosis was provided according to histopathological and IHC results followed by a confirmation of the primaries using radiological methods.

RESULTS

A total of 21 cases diagnosed with nonhematological solid tumor presented as lymph node enlargement between January 2013 and June 2016 were assessed retrospectively. The mean age was 57.23 y (range, 33–92 y), and 12 patients were males and 9 were females.

Clinical Approach

The localizations of the enlarged lymph nodes were inguinal (8 cases), axillary (6 cases), cervical (4 cases), and supraclavicular (3 cases). All patients applied with palpable mass, except 2 cases that were presented with inguinal pain and were diagnosed as prostatic adenocarcinoma and renal cell carcinoma.

All of the female patients (n=9) were assessed by breast and axillary examination followed by mammography and breast USG as the first step in the diagnostic approach. Male patients with axillary lymph node enlargement (n=2) were also examined using breast USG. Additionally, 3 cases were reported as those of metastatic epithelial tumor using fine needle aspiration cytology followed by the excision of the involved lymph node, and the final tumor type was evaluated by a histopathological assessment. None of the cases were diagnosed before the excision of the lymph node. No sarcomatous tumor was found among all the metastatic lymph nodes.

Histopathological Evaluation and IHC Analysis

The most common metastatic tumor presented with LAP was malignant melanoma (n=6; Figure 1a and 1b), followed by breast carcinoma (n=4; Figure 1c and 1d), squamous cell

Table 1. Characteristics of metastatic lymph nodes

Age (y)	Sex	Localization	Symptom	Diagnosed primary
79	Male	Supraclavicular	Palpable mass	Squamous cell carcinoma
64	Male	Supraclavicular	Palpable mass	Squamous cell carcinoma
33	Male	Axillary	Palpable mass	Malignant melanoma
63	Male	Cervical	Palpable mass	Malignant melanoma
62	Male	Supraclavicular	Palpable mass	Malignant melanoma
76	Male	Axillary	Palpable mass	Malignant melanoma
42	Male	Inguinal	Palpable mass	Germ cell tumor
50	Male	Inguinal	Palpable mass	Malignant melanoma
38	Male	Inguinal	Inguinal pain	Renal cell carcinoma
78	Male	Inguinal	Inguinal pain	Prostate adenocarcinoma
86	Male	Inguinal	Palpable mass	Urothelial carcinoma
45	Male	Inguinal	Palpable mass	Germ cell tumor
34	Female	Axillary	Palpable mass	Breast carcinoma
92	Female	Axillary	Palpable mass	Breast carcinoma
41	Female	Cervical	Palpable mass	Breast carcinoma
62	Female	Inguinal	Palpable mass	Endometrial adenocarcinoma
40	Female	Cervical	Palpable mass	Malignant melanoma
63	Female	Inguinal	Palpable mass	Ovarian serous carcinoma
56	Female	Axillary	Palpable mass	Ovarian serous carcinoma
36	Female	Axillary	Palpable mass	Breast carcinoma
62	Female	Cervical	Palpable mass	Papillary thyroid carcinoma

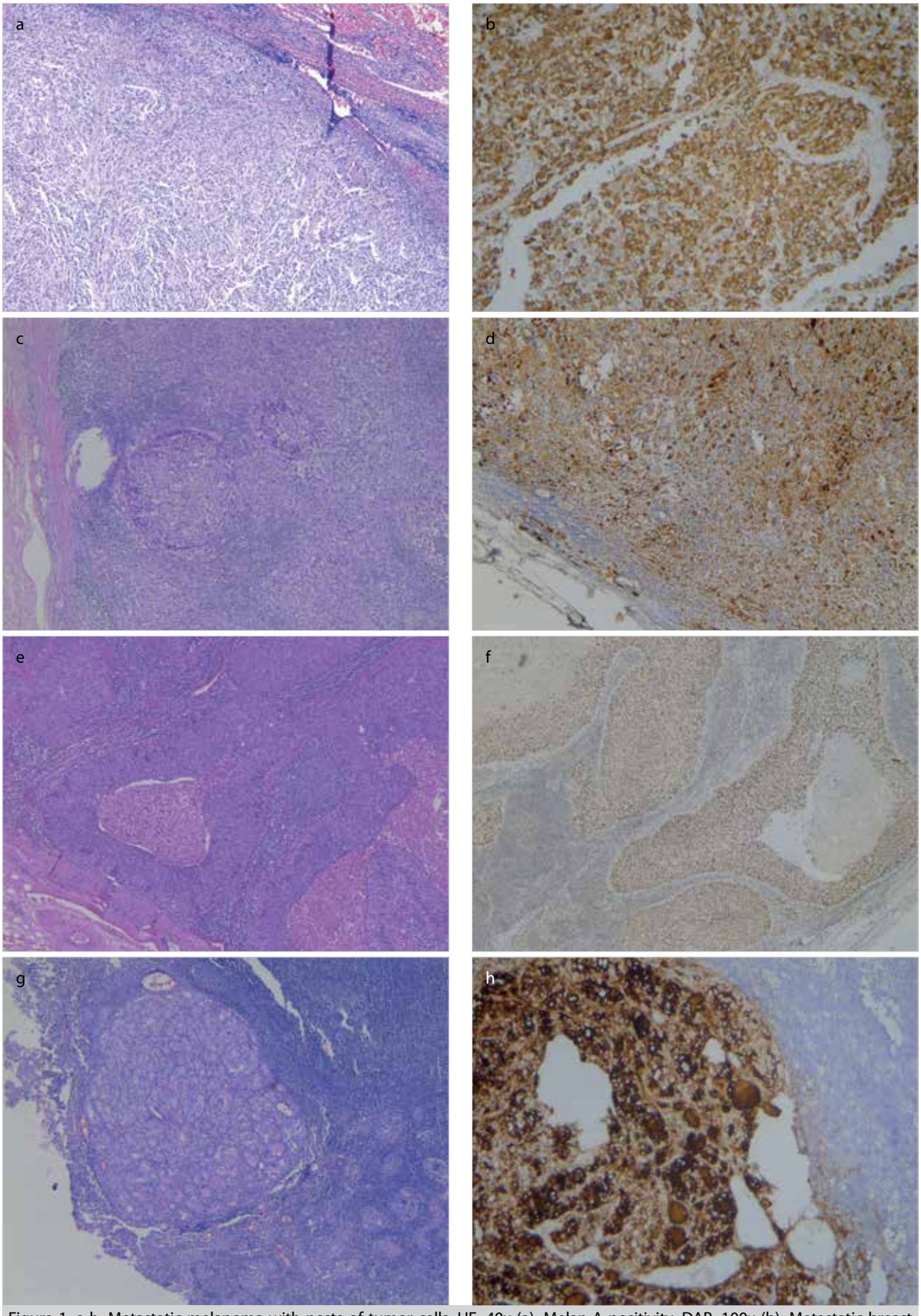

Figure 1. a-h. Metastatic melanoma with nests of tumor cells, HE, 40x (a); Melan-A positivity, DAB, 100x (b); Metastatic breast carcinoma, sheets of tumor cells , HE, 40x (c); GCDFP-15 positivity, DAB, 40x (d); Metastatic high grade urothelial carcinoma, HE, 40x (e); GATA-3 positivity, DAB, 40x (f); Metastatic papillary thyroid carcinoma, HE, 40x (g); Thyroglobulin positivity, DAB, 100x (h)

Table 2. Histopathological and immunohistochemical features of the metastatic tumors

Primary tumor	Histological features	IHC features	Additional parameters
Melanoma	Tumoral nests of cells with conspicuous nucleoli and numerous mitotic figures	HMB-45(+), S100 (+)	Melanin pigment (+)
Breast carcinoma	Tubules and solid tumoral areas	GCDFP-15 (+), CK 7(+), ER/PR (+)	-
Squamous cell carcinoma	Tumoral squamous cell nests with keratinization and keratin pearls	p63(+), HMWCK(+), CK20(–), TTF-1(–)	-
Prostatic adenocarcinoma	Cribriform malignant glandular structures	PSA (+),AMACR(+), CDX2(–)	Gleason score 4+4 (Grade group 4)
Papillary thyroid carcinoma	Tumoral cells showing papillary configuration with ground glass nuclei, nuclear grooves, and overlap	TTF-1(+), CK7(+), Thyroglobuline (+)	-
Ovarian carcinoma	Tubular, adenoid, and papillary configuration of pleomorphic tumoral cells showing conspicuous nucleoli	CK7 (+), WT1 (+), CA125 (+), CK20 (–), TTF-1 (–), CDX2 (-), GCDFP-15 (–)	-
Renal cell carcinoma	Tumoral cell nests with clear cytoplasm and conspicuous nucleoli	EMA (+), CD10 (+), Vimentin (+), PAX8 (+), CK7 (–), PSA (–), CDX2 (–)	-
Germ cell tumors	Cords and sheets of uniform but malignant cells surrounded with lymphocytic infiltration	OCT 3/4 (+), CD117 (+), PLAP (+)	-
Endometrioid adenocarcinoma	Epitheloid tumor characterized by solid sheets of round cells showing prominent nucleoli	pan CK (+), Vimentin (–), ER (+)	-
Urothelial carcinoma	Tumoral cords and columns with cells showing conspicuous nucleoli and hyperchromatic nuclei	CK 20 (+), GATA3 (+), Uroplakin III (+), CK7 (–), HMB45 (–), PSA (-), TTF-1 (–), OCT 3/4 (–), CDX2 (–)	-

HMB45: Human melanoma black-45; GCFDP-15:Gross cystic disease fluid protein-15; CK7: cytokeratin 7; ER: estrogen receptor; PR: progesterone receptor; HMWCK: high molecular weight cytokeratin; CK20: Cytokeratin 20; TTF-1: thyroid transcription factor-1; PSA: prostate specific antigen; AMACR: Alpha-methyl CoA Racemase; CDX2: Cluster of differentiation X2; WT1: Wilms tumor 1; CA 125: cancer antigen 125; EMA: epithelial membrane antigen; CD 10: Cluster of differentiation 10; PAX 8: Paired box gene 8; OCT 3/4: octamer-binding transcription factor 3/4; CD117: Cluster of differentiation 117; PLAP : placental alcaline phosphatase; Pan CK: pancytokeratin; GATA 3: GATA Binding Protein 3

carcinoma (SCC; n=2), and ovarian carcinoma (n=2). Other metastatic tumors were urothelial carcinoma (Figure 1e and 1f), papillary thyroid carcinoma (Figure 1g and 1h), renal cell carcinoma, prostatic adenocarcinoma, endometrial adenocarcinoma, and germ cell tumor (n=2).

Malignant melanoma as the most common metastatic tumor metastasized to axillary (n=2), cervical (n=2), inguinal (n=1), and supraclavicular (n=1) lymph nodes. Other tumors and involved lymph nodes are given in Table 1. Histopathological characteristics and IHC features are summarized in Table 2. Frequencies and descriptive statistics were done by SPSS software v20, IBM, USA.

Clinical Evaluation and Radiological Findings After Histopathological Diagnosis

None of the cases diagnosed with metastatic melanoma underwent detailed dermatological examination. After the diagnosis, only one case had a scalp lesion and the excision of the lesion showed melanoma with a Clark level of IV and a Breslow thickness of 2.4 cm. Other metastatic melanoma cases had no primary foci and were accepted as burnout primaries.

None of the female patients with axillary lymph nodes had any breast lesion detected by USG and mammography before the excision. After the diagnosis, all metastatic breast carcinoma cases had breast magnetic resonance imaging (MRI) and mammarian masses were detected with sizes in the range of 1.2–1.8 cm.

The cases with SCC had high-resolution lung CT and/or PET/CT for detecting the primary foci. One of the cases had shown lung primary and the other case had a 5 cm mass located in the renal pelvis biopsied using ureterorenoscopy and diagnosed as high-grade urothelial carcinoma with extensive squamous differentiation.

Metastatic ovarian carcinomas showed bilateral lobulated, contrasted cystic masses with sizes of 23×34 mm and 46×61 mm in the ovarian region on PET/CT. After the operation, the final diagnosis was ovarian serous carcinoma. Another case presented with axillary lymph node involvement had negative results in mammography and breast MRI, and the excision of the lymph node was performed with a suspicion of hematological malignancy. However, after the diagnosis of metastasis, the PET/CT showed a heterogenous cystic lesion of 5.5 cm size in the left ovarian region and extensive intra-abdominal metastatic lymph nodes, and the diagnosis was confirmed after the operation as ovarian high-grade serous carcinoma.

A 50-year-old female patient with axillary metastasis was investigated using mammography and breast USG; however, no mass was detected. After the excision of the lymph node with a suspicion of metastasis of occult breast carcinoma, the final diagnosis was of metastatic ovarian serous carcinoma. The diagnosis was confirmed by lower abdominal CT showing left ovarian cystic mass, which was operated and diagnosed as ovarian serous carcinoma with a size of 44×32 mm and having a thin septae.

The case of metastatic urothelial carcinoma was then confirmed by cystoscopic samples of highgrade urothelial carcinoma with muscularis propria and extensive urothelial carcinoma in situ.

The case of papillary thyroid carcinoma was examined using USG and diagnosed as multinodular goiter with a maximum size of the nodule as 1.2 cm. The fine needle aspiration biopsy (FNAB) performed upon both the thyroid and the lymph node was benign, and the lymph node was subsequently excised. After the diagnosis of the metastatic lymph node, total thyroidectomy was performed and papillary carcinoma was diagnosed at three different foci with a maximum size of 1.2 cm showing capsular invasion. The case applied with inguinal pain was operated for inguinal hernia, and an enlarged lymph node was detected during the operation. After the diagnosis of metastatic prostatic adenocarcinoma, rectal examination revealed enlarged, hard prostatic tissue with a slight increase of prostatespecific antigen (PSA; 4.7 ng/mL).

A 38-year-old male applied with inguinal pain, and the enlarged inguinal lymph node was excised because of the suspicion of a hematological malignancy. After the diagnosis of metastatic renal cell carcinoma, detailed imaging studies revealed a cortical, 3.8 cm-sized, solid renal mass located in the upper lobe of the right kidney. After radical nephrectomy, a clear cell renal cell carcinoma of Fuhrmann grade 3 with vascular invasion was detected.

In one of the 2 cases of metastatic germ cell tumor, a 2.4 cm-sized mixed germ cell testicular tumor (seminoma, 70%; embryonal carcinoma, 30%) with necrosis was detected through orchiectomy. The other case showed a fibrohyalinized nodule located in the right testis with no alive tumor cells. The morphological features were concordant with burnout tumor.

DISCUSSION

Nonhematological malignancies presenting with lymph node enlargement are one of the most confusing cases for clinicians. A standard diagnostic approach for enlarged lymph nodes should consider detailed medical history, physical examination, clinical symptoms and findings, laboratory and imaging studies, and histopathological evaluation using IHC analysis (2).

Radiological studies have diagnostic limitations of about 30%–50% for various tumor types (3). However, MRI has a chance of tumor detection of about 70% in axillary metastasis (4). Fluorodeoxyglucose (FDG) PET, which has an important role in investigating metastasis of malign tumors, has various detection rates in primary unknown tumors (PUT) with the most common being lung (5) and head and neck cancers of about 50%. There are studies supporting that FDG PET/CT is better in detecting primary tumors. In a study, a rate of 55% was reported for FDG PET/CT, whereas 31% for FDG PET in cervical lymph node enlarged patients (6, 7). In another meta-analysis, the detection rate of FDG PET/CT was 37% with the most common primary being lung (33%) (8). In another study, 28.5% of metastatic cases were unable to locate the primary foci using FDG PT/CT (9). In some centers, otorhinolaryngologists particularly use routine PET/CT for lymph node enlargements in the head and neck region (10).

The limitations of radiological methods redirect clinicians to pathological evaluation. Because many different targeted drugs were being used for different tumor types, finding the exact primary focus of the metastatic tumors is necessary in oncology practice. One of the most definitive results may be accomplished by a histological examination.

The histopathological assessment of excisional lymph node biopsies is cost effective in patients with metastatic lymph nodes and who were being investigated for primary tumors. In these patients, the tumor can only be diagnosed by the histopathological evaluation of the enlarged lymph node, which also excludes hematological malignancies (11). These excisional biopsies may be the only way for determining treatment protocols and prevent patients from more invasive procedures.

Tru-cut, incisional, or open biopsy can provide material for histopathological evaluation; however, total excision of the lymph node with intact capsule is the gold standard for pathological analysis (1). FNAB is relatively useful for epithelial tumors, but excisional biopsies are more important as they enable better samples for tumor morphology as well as IHC and histochemical analysis (12). As epithelial tumors metastasize lymph nodes from subcapsular sinuses, total excision with intact capsule is much more important for pathological evaluation. However, lymph node excision is a procedure and we know that every operation has its own risks due to anesthesia or the procedure itself. Therefore, the decision for lymph node excision should be considered based on all the aspects of the patient.

As the most common subtypes of PUT are unspecified adenocarcinomas, undifferentiated adenocarcinomas, and poorly-differentiated tumors, it is very important to specify the primary focus of the metastatic disease. The general pathological algorithmic approach for differentiating metastasis is to decide whether the tumor is epithelial, lymphoid, sarcomatous, or melanoma. Although there is no worldwide accepted guidelines for pathological analysis, it is commonly advisable to start with vimentin, Cluster of Differentiation (CD) 45, HMB-45, and pancytokeratin (2, 13, 14). Many and different antibodies can be used for IHC; however, sometimes overlapping results may complicate suggestions for primary tumors. In cases with a general impact of epithelial tumor metastasis, CK 7 and CK 20 may be chosen as the first step (15). In all of our cases, the diagnostic approach was initiated with pancytokeratin, vimentin, and CD45 to decide the nature of the tumor.

Antibodies specific for an organ or a tumor type can be added due to histological findings (such as PLAP and OCT ¾ for germ cell tumors; chromogranin A, synaptophysin, and CD 56 for neuroendocrine tumors; PSA and PSAP for prostatic origin; mammoglobin and GCDFP-15 for breast origin; CDX2 for intestinal origin; WT1 and CA-125 for ovarian cancers; TTF-1 for lung and thyroid cancer; and thyroglobulin for thyroid origin). Despite the fact that all tumor types may not have a definite specific antibody, IHC analysis is advantageous among many imaging methods due to its cost-effectiveness (2, 12, 16). We also used specific antibodies, such as thyroglobulin, CA125, CD X2, WT1, and GCDFP15, for detecting the primary foci.

The necessity for molecular diagnostic methods cannot be denied because gene expression profiles have an important role in tumor classification according to literature (17, 18) However, the accessibility to gene profiling methods can be impossible for small scale hospitals and this impossibility increases the importance of histopathological evaluation and IHC analysis of the excisional biopsies in especially small centers.

Even by using many diagnostic modalities, some of the metastatic cases remain as primary unknown tumors, forming the fourth most common cause of death (1).

The first-step diagnostic approach must include IHC markers that may help to decide if the tumor is epithelial, sarcomatous, lymphoid, or melanoma. In cases of melanoma and germ cell tumors, it is important to remember that the primary tumor can be "burnout". The diagnosis of the primary tumor from the histopathological evaluation is important for clinical, prognostic, and treatment protocols especially for tumors of which primary focus can be regressed spontaneously. As observed from our results, melanoma is the most common metastatic tumor with unknown primary focus. In 6 cases (28.5%), melanoma was diagnosed due to its metastasis.

Molecular DNA profile studies added to pathological evaluation increases the diagnostic rate up to 80%. However, the high cost and inapplicability of molecular studies at every center emphasize the accessibility and cost effectiveness of routine pathological examination and IHC analysis.

CONCLUSION

Nonhematological malignancies presenting with LAP are one of the most complicated cases for clinicians. In cases presenting with LAP without a primary focus found by simple radiological methods, the primary tumor can be diagnosed by a histopathological evaluation of the metastatic lymph nodes. The histopathological evaluation of the excisional metastatic lymph node biopsies is an important method due to cost effectiveness and easy applicability.

Ethics Committee Approval: Not required in this study.

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

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