Unexpected findings in the neck dissection specimens for primary head and neck squamous cell carcinoma

Primer baş ve boyun squamöz hücreli karsinomlarında boyun diseksiyonu örneklerinde beklenmedik bulgular

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Objectives: We aimed to determine the incidence of unexpected pathological findings observed during the histopathological examination of the neck dissection specimens performed for primary head and neck squamous cell carcinoma. and their impacts on the treatment and follow-up plans.

Patients and Methods: We retrospectively reviewed 410 patients (369 males, 41 females; 169 patients unilateral, 241 patients bilateral) with a diagnosis of squamous cell carcinoma of head and neck, who underwent 651 neck dis-

Results: Unexpected pathological findings were found in 3.2% of patients and 2% of neck dissections. These unexpected findings were tuberculosis in eight patients (2%), metastatic papillary thyroid carcinoma in three patients (0.7%), Warthin's tumor in one patient and cystic hygroma in one patient. All patients who had metastatic papillary thyroid carcinoma received radioactive iodine treatment after thyroidectomy. In control examinations, none of these cases had problem related to neither primary disease nor thyroid pathology. Only two of eight patients who had tuberculosis in lymph nodes received medical treatment for tuberculosis, while the others were observed by clinical and radiological examinations. None of these patients had problems related to tuberculosis. We had no long-term follow-up results for cystic hygroma and Warthin's tumor since these patients did not continue their routine examinations.

Conclusion: During the pathologic examination of neck dissections, unexpected pathologic findings may occasionally be encountered. Most frequently seen unexpected findings were tuberculosis lymphadenitis and metastatic papillary thyroid carcinoma. However, these pathologic findings do not seem to affect the management of the primary disease.

Key Words: Head and neck neoplasms; neck dissection; squamous cell carcinoma.

Amaç: Primer baş-boyun yassı hücreli karsinomu nedeniyle yapılan boyun diseksiyonunda elde edilen örneklerin incelenmesi sırasında karsılasılan beklenmedik patolojik bulguların ve görülme sıklığının, takip ve tedavi süreci üzerine etkileri ortava kondu.

Hastalar ve Yöntemler: Primer baş-boyun yerleşimli yassı hücreli karsinom nedeniyle 410 hastaya (369 erkek, 41 kadın; 169'u tek taraflı, 241'i iki taraflı) yapılan toplam 651 boyun diseksiyonuna ait bilgiler hasta dosyalarında geriye dönük olarak incelendi.

Bulgular: Olguların %3.2'sinde, boyun diseksiyonlarının ise %2'sinde beklenmedik patolojik bulgu saptandı. Beklenmedik bulgu olarak, sekiz olguda (%2) granülomatöz iltihap (tüberküloz ile uyumlu), üç olguda (%0.7) papiller tiroid karsinomu yayılımı, birer olguda ise Warthin tümörü ve kistik higroma vardı. Tiroid papiller karsinomu saptanan olguların tümü tiroidektomi sonrası radyoaktif iyot tedavisi aldı. Bu olguların izlemlerinde primer tümör ve tiroid karsinomuyla ilgili sorun saptanmadı. Tüberküloz saptanan sekiz olgunun ikisi dısındakilere tüberküloz tedavisi verilmedi ve klinik takibe alındı. Bu hastaların hiçbirinde tüberküloz ile ilgili sorunla karşılaşılmadı. Kistik higroma ve Warthin tümörü saptanan olguların takiplere gelmemeleri nedeniyle uzun dönem takip sonuçları elde edilemedi.

Sonuc: Primer bas-boyun yassı hücreli karsinomu nedeniyle yapılan boyun diseksiyonlarında ender de olsa beklenmedik bir başka patolojiye ait bulgular saptanabilir. Bu patolojiler içinde en sık rastlananları, tüberküloz lenfadenit ve tiroid papiller karsinom metastaz yayılımıdır. Ancak bu patolojilerin primer tümörün tedavi sürecini çok fazla etkilemediği düşünülmektedir.

Anahtar Sözcükler: Baş-boyun kanseri; boyun diseksiyonu; yassı hücreli karsinom.

Therapeutic or prophylactic neck dissection constitutes a critical part of the treatment in patients who underwent surgery for primary squamous cell carcinoma (SCC) of the head and neck. Pathological examination of the tissues removed during this procedure (both the tumor and the neck dissection specimens) aids to stage the disease and the physicians decide whether or not additional treatment is required. During these examinations, in addition to the findings pertaining to the known tumor, findings pertaining to clinically unknown or unsuspected coexistent diseases may be observed in the neck dissection specimens.[1,2] These findings can be related to aberrant tissues or cysts secondary to embryological migration disorders, as well as a coexistent, clinically dormant infectious, inflammatory or malignant pathology.[2-9] These unexpected findings observed in neck dissection specimens are critical for the success of the treatment since they affect the timing and nature of postoperative oncological treatments, survival rate, and quality of life.[1]

Numerous studies were carried out on treatment strategies in SCC of the head and neck. However, we do not have sufficient data on the frequency of unexpected coexistent pathologies identified during the treatment of the primary disease and how to proceed with the treatment when such pathologies are detected. With this study, we present the unexpected findings identified in neck dissection specimens and our approach in a homogenous group of patients with SCC of the head and neck.

PATIENTS AND METHODS

Medical charts and pathological reports of 451 patients who had prophylactic or therapeutic neck dissection for SCC of the head and neck over a 10-year period between January 1995 and December 2004 in the Department of Otorhinolaryngology-Head and Neck Surgery of Uludağ University School of Medicine were reviewed retrospectively. Patients with any histopathological diagnosis other than SCC or those who had neck dissection for cervical metastasis of SCC localized outside of head and neck were excluded from the study. A total of 41 patients operated on for SCC of the head and neck whose medical charts or pathological reports were missing, patients whose primary mode of treatment was not surgery and those who had chemotherapy or radiotherapy to the neck prior to the operation were also excluded from the study.

Four hundred and ten patients who fulfilled these criteria were assessed. There were 369 males (90%) and 41 females (10%). One hundred and sixty nine patients (41.2%) had unilateral and 241 (58.8%) had bilateral neck dissection. Therefore, pathological specimens obtained from 651 neck dissections were examined for pathological findings. Of the neck dissections, 250 (38.4%) were comprehensive (CND) and 401 (61.6%) were selective neck dissections (SND).

All pathological findings found during the pathological examination of the neck dissection material except those related to the cervical metastasis of the primary tumor or a preoperatively known coexisting disease, were accepted as "unexpected finding". Medical charts of these patients were re-reviewed in detail to reveal our approach to the unexpected disease and the primary SCC of the head and neck, and oncological status of the patients in last visit were established. Approval for this study was obtained from the Ethics Committee of the Faculty of Medicine of Uludağ University.

RESULTS

As expected, pathological examination of the neck dissection specimens revealed cervical metastases in 180 patients (43.9%) of the primary SCC of the head and neck. Twenty-eight (15.5%) of these metastases were bilateral. An unexpected finding was observed in 3.2% of the patients (13/410) and 2% (13/651) of neck dissections. The unexpected findings were granulomatous inflammation in eight patients (2%), metastasis of papillary thyroid carcinoma (PTC) in three patients (0.7%), Warthin's tumor in one case, and cystic hygroma in one patient. Detailed clinical information on our patients is presented below:

Patients with papillary thyroid carcinoma metastasis:

Pathological examination of the material obtained from a patient who underwent total laryngectomy (TL) + bilateral SND (levels II-III-IV-VI) + right total and left subtotal thyroidectomy for $T_3N_0M_0$ glottic laryngeal SCC revealed cervical metastasis of SCC to three lymph nodes in level II and cervical metastasis of PTC to a lymph node in level VI. Primary tumor could not be found in the thyroidectomy specimen. Adjuvant radiotherapy (RT) covering whole neck and complementary thyroidectomy was recommended as a result of three metastatic lymph nodes in level II. The patient did not give consent

to the recommended surgery and/or RT. Following the treatment of deep anemia and pneumonia, the patient was given radioactive iodine (RAI) at the postoperative fifth month. No recurrence of the primary disease or a thyroid malignancy-related problem was noted during 42-month follow-up.

Pathological examination of neck dissection contents of a patient who had TL + right CND + left SND (levels II-III-IV) for T₃N₁M₀ supraglottic laryngeal SCC showed no signs of SCC metastasis to the cervical lymph nodes. However, PTC metastasis at the level II node was diagnosed. The patient received total thyroidectomy. Focus of primary tumor could not be identified with the thyroid gland during pathological examination. Following endocrinology consultation, RAI treatment was recommended and given at the postoperative sixth month. No pathological findings related to the primary disease or PTC were observed during 40-month follow-up.

A patient with $T_2N_0M_0$ supraglottic laryngeal SCC had supraglottic laryngectomy + bilateral SND (levels II-III-IV) and pathological examination showed no cervical SCC metastasis. However,

PTC metastasis was found in seven level III and two level IV nodes. Intraoperative frozen section examination at the surgical margin was negative; on the other hand, definitive report confirmed that the lower surgical margin was positive for cancer cells. For the primary laryngeal tumor, the patient was recommended additional resection and probable TL with total thyroidectomy followed by RAI treatment. The patient did not accept TL and additional intervention to larynx. Therefore, a right total and left subtotal thyroidectomy was performed. Pathological examination showed millimetric focus of tumor within the right thyroid lobe. Due to positive surgical margin, the patient was given RT, followed by RAI and the patient was free of any problems related to the primary disease or thyroid pathology within postoperative 84 months.

Patients with tuberculosis:

In 2% of the patients (8/410), unexpected finding was granulomatous inflammation consistent with tuberculosis (Tbc) of the lymph nodes. Preoperative bilateral chest radiographs of all these patients were normal. Only one of the eight patients with cervical

Table 1. A summary of the clinical details of patients with lymph nodes demonstrating changes consistent with tuberculosis

Case	Primary tumor	Surgical procedures	Additional treatment	Preoperative assessment/result	Tuberculosis found at	Extra evaluation	Tuberculosis treatment	Follow-up duration	Condition
1	T ₃ N ₁ M ₀ Larynx	TL + Bilateral CND + Left total thyroidectomy	RT	Consultation with pulmonologist/ treatment for COPD	5 lymph nodes at left level V	None	None	6 months	Healthy
2	T ₃ N ₀ M ₀ Larynx	TL + Left SND (2-3-4) + Left total Right subtotal thyroidectomy	RT I,	PA/Normal	7 lymph nodes (level unspecified)	None	None	45 months	Healthy
3	T ₄ N ₀ M ₀ Larynx	TL + Left CND	RT	PA/Normal	8 lymph nodes at levels III and IV	None	None	84 months	Healthy
4	T ₃ N ₀ M ₀ Larynx	TL + Left CND + Right SND (2-3-4)	RT	PA/Normal	1 lymph node at right level II	None	None	36 months	Healthy
5	T ₄ N ₀ M ₀ Larynx	SGL + bilateral SND (2-3-4)	RT	PA/Normal	1 lymph node at left level II	None	None	26 months	Healthy
6	Oral cavity	Hemiglossectomy + Left CND	7 RT	PA/Normal	4 lymph nodes (level unspecified)	None	None	2 months	Lost to follow-up
7	T ₄ N _{2a} M ₀ Larynx	TL+ Right CND + Left SND (2-3-4)		PA/Normal	8 lymph nodes at left level I p	Cons with oulmonologis	for 9 st months	18 months	Healthy
8	$T_4N_1M_0$ Larynx	TL+ Bilateral SND	RT	PA/Normal	1 lymph node at left level II	None	None	6 months	Died at 6th month

TL: Total Laryngectomy, CND: Comprehensive neck dissection, RT: Radiotherapy; COPD: Chronic obstructive pulmonary disease; SND: Selective neck dissection; PA: Posterior-anterior chest X-ray; SGL: supraglottic laryngectomy; T: Tumor; N: Lymph nodes; M: Metastasis.

Tbc were given extra medical treatment for Tbc. During their follow-up, the patients did not experience any problems related to their primary disease or Tbc. Four patients, who had cervical Tbc but did not have additional medical treatment, were normal during their follow-up (minimum follow-up: 7 months, maximum follow-up: 84 months). One patient died at the fifth postoperative month due to cardiac problems. Most recent health status of a patient is unknown since the patient was lost to follow-up after two months.

Clinical details of patients with lymph nodes demonstrating changes consistent with Tbc, as detected by examination of the neck dissection material, are summarized in Table I.

Other patients:

During the pathological examination, cervical metastasis of SCC was not identified in a patient who underwent TL + right SND (levels II, III, IV) + left CND for $T_3N_1M_0$ SCC of the larynx, but Warthin's tumor was found in the right neck dissection material. Additional examinations could not be carried out since the patient did not attend follow-up controls after one month.

Another patient had partial glossectomy + right CND for $T_2N_1M_0$ SCC of the tongue. Pathological examination showed cervical cystic hygroma. Squamous cell carcinoma metastasis was not observed. The patient did not attend the follow-up controls and therefore recent health condition could not be assessed.

DISCUSSION

Different studies about treatment regimens of SCC of the head and neck have been carried out and the results have been presented. However, our knowledge on the frequency of unexpected pathologies identified during the treatment of the primary disease and how to manage such pathologies is limited.

Studies by Ansari-Lari and Westra^[1] Sheahan et al.^[2] and Ratcliffe and Soutar^[10] reported unexpected findings in 5-11% of their cases during the pathological examination of the neck dissection specimens. These unexpected findings can be thyroid follicles, PTC metastasis, Tbc lymphadenitis, lymphoma, cervical metastasis of a coexistent malignant tumor which does not present a symptom, as well as a benign pathology.^[2] There is a second primary tumor in about 20% of patients with

a cancer of the head and neck region, and cervical metastasis of the second tumor may be identified during surgical procedures towards the clinically evident disease.^[4]

Cystic hygroma is a congenital benign malformation of the lymphatic system that presents itself during childhood. [11,12] Spontaneous regression is not uncommon. Therefore, conservative approach can be preferred unless there is malnutrition or respiratory problems. Surgical excision is mandated in cases with cosmetic problems, nutrition and/or respiratory problems and in those diagnosed at a later age. [11-13] Therefore, even though this patient was lost to follow-up, benign character of cystic hygroma and the fact that the lesion was totally excised during the neck dissection meant that there would be no need for an extra intervention.

Warthin's tumor is a benign tumor containing epithelial and lymphoid tissue elements. It is generally seen in the parotid gland and comprises 6-14% of all parotid neoplasms. It is also known as adenolymphoma and papillary cystadenoma.[14] Though rare outside the parotid gland, the most common occurrence is at the cervical lymph nodes and it is usually diagnosed unexpectedly during neck dissections for another tumor. [15] Despite being a benign pathology, there is a 0.06-0.3% risk of malignant transformation.[16] Treatment is total excision. In the present study, the unexpected finding was cervical Warthin's tumor that would not affect the oncological treatment process. Since physical examination of the patient did not reveal a mass lesion in the parotid gland, Warthin's tumor identified during the neck dissection was believed to arise from the lymph nodes. Additional treatment was not planned since it was totally excised.

Even though PTC comprises only 1% of all diagnosed cancers, subclinically, they are relatively frequent. Different rates have been reported in the literature but occult or subclinical PTC occurs in some 35.6% of adults and it is believed not to have an influence on survival. Thyroid tissue has been identified in 0.6-1.5% of neck dissections carried out for SCC of the head and neck. In addition to the view that a defect in thyroid tissue migration causes well-differentiated thyroid cells to remain within other tissues of the neck, some authors argued that all abnormally located thyroid tissues are due to a primary malignancy. Hence, there is a controversy as to whether thyroid tissue identified in the neck during surgical procedures for

other causes is related to cervical metastasis of an occult primary tumor or these tissues are benign ectopic tissues.^[3] An autopsy study by Meyer and Steinberg^[17] reported thyroid follicles in the lymph nodes of 5% of patients in the absence of a focus of malignancy in the thyroid gland. This suggests that well-differentiated thyroid tissues identified in the neck may be normal tissues with ectopic locations. Even though survival in primary PTC is satisfactory, how to approach an incidentally diagnosed case when there is another malignancy is an important issue.^[4]

During histopathological examination of 0.7% of our cases, we detected PTC metastasis that was not clinically evident. This rate is equal to 0.7% reported by Ansari-Lari and Westra^[1] in a comparable study. In our clinic, dissection of level VI during SND, the most common site of metastasis of thyroid malignancies, is carried out when laryngeal tumors extend towards subglottis, when tracheostomy was opened before the surgery and when a lesion is detected radiologically at level VI. Due to the fact that the central lymph nodes that is the primary site of metastasis of thyroid cancers were not sampled in the majority of the cases included in our study and 41.2% of the neck dissections were unilateral, this ratio can be lower than actual ratio. However, even though various autopsy studies reported the incidence of cervically located foci of occult thyroid cancer to vary between 6 and 35.6%, when compared to this disease which is responsible in 1.6% of newly-diagnosed cancer patients and 0.2% cancer-related mortalities, there is a debate on the management.[18,19] When we reviewed the literature, we noticed that some of the patients with incidentally found cervical PTC metastasis did not only receive a treatment for this, but also did not have a problem related to thyroid malignancy as well.[1,4,17] Survival in primary tumors arising from the thyroid is considerably high; a 20-year survival is expected to be around 80%. It is the biological behavior of the SCC of the head and neck that determines the survival. However, it should be noted that, if cure is achieved for the primary disease, untreated thyroid malignancies can decrease the life expectancy of patients followedup for primary SCC of the head and neck and found to have PTC metastasis as an unexpected finding.[4] Papillary thyroid carcinoma, as an unexpected finding, was detected in three patients in our series. Essentially, we planned the treatment for the primary disease since that directly affects

the life expectancy in these patients. Incidentally found PTC did not alter the process of the treatment of the primary disease.

Tuberculosis was thought to be under control in developed countries but recent changes in its clinical course and resistance to anti-tuberculosis drugs meant that it has once again become a serious health issue^[5] and according to World Health Organization data, one third of the world's population is infected with Tbc.[8] The most common extrapulmonary site of involvement of Tbc is the lymph nodes, particularly the nodes of the head and neck. [5,6,20] Extrapulmonary Tbc involving the neck is usually unilateral.[6] With an ongoing increase in its frequency of occurrence, experience of otorhinolaryngologists is rather limited.[7] Another reason why high risk of occurrence of Tbc in the head and neck region, especially in immune compromised individuals, raises concern is the increase in malignancies in the head and neck region. Malignancy in the body causes a decrease in the cellular immunity response, the most important defense mechanism of humans against Tbc, which, in turn, facilitates infection. [9] Cervical Tbc in patients followed-up for primary pulmonary Tbc is caused by the release of the bacilli from the primary focus into the lymphatic circulation. [6] In extrapulmonary Tbc cases, classical symptoms of Tbc, such as fever, night sweating and weight loss, are less prominent and the frequency of concomitant pulmonary Tbc is reported to be 16-40%. [5] Therefore, isolated extrapulmonary Tbc is more difficult to diagnose.^[5,7] Geldmacher et al.^[7] showed that in 15% of the patients, sputum microscopy was negative for the disease though the bacilli grew in culture in eight weeks. Chest radiographs of all patients were normal.

Successful results can also be achieved in extra-pulmonary Tbc cases with antituberculosis drugs. When medical treatment fails, wide surgical excisions such as neck dissection can be tried to confirm the diagnosis, treat and assess the drug resistance. [5,6] In a study by Weiler et al., [21] the authors reported that surgical excision was required in 76.1% of the patients followed-up for cervical Tbc due to unresponsiveness to medical treatment and total cure was achieved following surgery. Manolidis et al., [22] on the other hand, argued that surgical excision was required in 90% of the patients with cervical Tbc refractory to medical treatment.

Granulomatous inflammation consistent with Tbc in the cervical lymph nodes was found in 2% of the cases in our series. Previously, Sheahan et al.[2] reported this ratio as 1%. In our series, only two of the eight cases with cervical Tbc had additional medical treatment for Tbc. During follow-up, these patients did not have any complaints related to the primary disease or Tbc. Four patients with cervical Tbc who did not have any Tbc treatment were found to be healthy at follow-up. One patient died of cardiac causes at the postoperative sixth month, while the remaining patient could not be assessed due to non-attendance to follow-up control appointments after two months. Our clinical practice, not giving additional treatment to those with cervical Tbc and not carrying out further examinations for Tbc, can be criticized. However, it was already reported that a primary pulmonary focus could not be identified in 44% of the cases with Tbc of the cervical lymph nodes. [7] Ammari et al. [6] argued that obtaining good quality chest radiographs was sufficient to search for primary pulmonary focus in patients diagnosed with cervical Tbc. Therefore, assessed by radiologists, preoperative frontal and lateral chest radiographs may suffice. Preoperative posteroanterior chest radiographs of eight patients diagnosed with Tbc were assessed by the Department of Radiology and no pathology was reported. Wide excision yields satisfactory results in Tbc lymphadenitis cases refractory to medical treatment.[21,22,23] Excision of the probable regions of involvement in the neck by neck dissection was carried out as part of the treatment of the primary disease and no problems with regard to Tbc were encountered during follow-ups. Even though our sample size was small, when supplemented by literature data, it may be possible to conclude that close clinical follow-up is sufficient in cases with incidental finding of cervical Tbc unless another focus is detected. However, during clinical follow-up of the patients, it would be a wise decision to enlist the help of a physician experienced in Tbc, preferably a pulmonologist, and follow up the patient together.

In conclusion, neck dissections are frequently carried out for the treatment of SCC of the head and neck and during these dissections, pathological findings related to an unsuspected disease other than the metastasis of the known primary tumor may be encountered. This unexpected pathological finding is often Tbc or papillary thyroid cancer metastasis to the cervical lymph nodes. However,

these unexpected pathologies rarely affect the planning of the course of treatment of the primary SCC of the head and neck. When Tbc is observed as an unexpected finding during neck dissections, extra intervention may not be necessary except close clinical follow-up if frontal and lateral chest radiographs of the patient are normal. If PTC is diagnosed, management of this disease should be planned following the treatment of the primary disease.

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