Clinics in Oncology

Research Article
Published: 06 May, 2022

Non-Keratinizing Squamous Cell Carcinoma in the Tongue

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Abstract

Objectives: This study aimed to know the clinical-pathological features of the Non-Keratinizing Squamous Cell Carcinomas (NKSCCs) arising in the tongue, classify them microscopically, and analyze their behavior, treatment and prognosis. Also, we challenge the opinion that NKSCCs histology strongly predicts HPV-association; comparing the clinicopathological findings of non-HPV tested NKSCCs with data from previously reported HPV-positive cases.

Study Design: We selected all NKSCCs from the files of the Surgical Pathology Service at the Hospital General de México. Their clinicopathological data and slides were retrieved, analyzed, and compared with previously reported series of cases.

Results: Sixty percent of the analyzed tumors were in men (mean age = 56.5 years). Mean age was higher in men than in women, 33.3% of tumors invaded the floor of the mouth and 23.3% the submandibular salivary gland; 66.6% were T1-T2 tumors followed by T4 tumors for which the mean age was younger; 33.3% presented lymph node involvement. Microscopically, NKSCCs displayed well-defined morphological features and a non-keratinizing basal cell-like component as their main cytological feature. Two variants were found, the NKSCC and the hybrid-Squamous Cell Carcinoma (SCC). Hybrid SCCs comprised 83.3% of the neoplasms and were the most aggressive tumors, having more recurrences, presenting higher T scores and staging, and were the only tumors showing lymph node involvement. Tumors recurred more frequently in men and were more frequent in patients older than 50 years.

Conclusions: 1) Clinicopathological features and behavior of NKSCCs without HPV tests were similar to those previously published with HPV-positivity supporting the suggestion that adjuvant testing is not necessary since 100% of the NKSCC are p16 positive. 2) Hybrid SCCs were more common than NKSCCs. 3) Only hybrid SCCs developed lymph node involvement. 4) NKSCCs have a less aggressive behavior and better prognosis than hybrid SCCs. 5) NKSCC microscopic features support the suggestion that its histology could predict HPV-association and these attributes are more important in prediction of outcome.

Keywords: Squamous cell carcinoma; Head and neck; Tongue; Non-keratinizing carcinoma

Introduction

The WHO defines the Oral Squamous Cell Carcinoma (OSCC) as "a carcinoma with squamous differentiation arising from the mucosal epithelium" [1]. The most pivotal malignancy of the oral cavity and mobile tongue is the OSCC, since more than 90% of the oral cancers correspond to these neoplasms [2]. Anatomically, the tongue is composed of two parts, the mobile tongue located in the oral cavity, and the base of the tongue located in the Oropharynx (OP). Both parts, the oral portion (anterior or mobile tongue) and the base of the tongue are physically distinct and are anatomically different and each one has different tissular composition. For the above-mentioned reasons, neoplasias arising in both parts are different in behavior, prognosis, and cellular composition. The base of the tongue is part of the OP and, as the nasopharynx, is characterized by the presence of lymphoid mucosa covered by the reticulated epithelium possessing a discontinuous basement

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Received Date: *07 Apr 2022*
Accepted Date: *02 May 2022*
Published Date: *06 May 2022*

Citation:
Juan Carlos H-G, Soares CD, Jimenez-Farfan, Dolores M, Luis Uriel R-B, Lara Gutiérrez CA, et al. Non-Keratinizing Squamous Cell Carcinoma in the Tongue. Clin Oncol. 2022; 7: 1913.

ISSN: 2474-1663

membrane (also known as lymphoepithelium). In contrast, the epithelium covering the surface of the oral portion of the tongue is squamous, stratified, and keratinized [3,4]. For this reason, neoplasias arising in both portions of the tongue show contrasting microscopic features, different behavior, and prognosis, and their management also varies.

According to El-Mofty et al. [5], Squamous Cell Carcinomas (SCCs) arising from the base of the tongue manifest two main microscopic features. The first is the so-called conventional SCC, now named Keratinizing SCC (KSCC) composed of mature "keratinizing epithelium". The other kind of SCC is characterized by the presence of sheets, nests, or trabeculae of oval and, frequently, spindled hyperchromatic cells lacking prominent nucleoli and indistinct cell borders, commonly regarded as "basaloid cells". This malignancy is the Non-Keratinizing SCC (NKSCC). An intermediate entity is the "mature keratinizing" or hybrid SCC, consisting in a mixture of both features. As in the NKSCC, in the hybrid variant the basal cell component is the main feature, complemented with >10% islands of keratinizing cells.

In the 2005 WHO classification of tumors of the oral cavity and OP, differentiation between KSCC and NKSCC was not considered [6], and in the 2017 edition of the WHO Blue Book an advance was achieved, and two different types of carcinomas were described. One is the HPV-positive SCC, microscopically it exhibits a non-keratinizing morphology that rarely shows dysplasia of the surface epithelium, suggesting it is a separate neoplasia. The second entity is the HPV-negative SCC, it shows microscopic features similar to the well-known, classical, conventional KSCC [7].

The NKSCC is a rare tumor more commonly found in the OP, considering it develops from malignant transformation of the reticulated epithelium covering the tonsillar crypts. Interestingly, we found recent reports on NKSCC examples developing in other anatomical areas covered or containing several types of epithelium different to the reticulated type, like the larynx, nasopharynx, sinonasal tract, paranasal sinuses, thymus, lungs, conjunctiva, lacrimal sac, vulva, penis, anus, and other sites [8-14]. To date, all reported oropharyngeal NKSCCs have been HPV-positive neoplasms with high K and low p53 scores. Considering that all the oropharyngeal NKSCCs are always HPV-positive, different authors suggested that light-microscopic features of NKSCC could diagnose HPV-related SCC [5,8,11-13,15-20]. Chernock et al. [16] concluded that the microscopic features of the NKSCC strongly predict HPV-association.

Clinicopathological features of the NKSCCs of the OP are well studied in the literature and data on the cases involving the tongue are mixed with data of NKSCCs arising in other oropharyngeal sites. To date, no clinicopathological information on NKSCCs arising in the tongue tissues is available in the literature. The aims of this study were to analyze the NKSCCs attributes under a different viewpoint to know the clinical-pathological features of the NKSCCs arising in the tongue, typify these examples according to the El-Mofty et al. [5] classification, and to analyze their behavior, treatment, and prognosis. Also, in view that all NKSCCs reported in the literature were HPV-positive neoplasms, we decided to challenge the previously reported opinion that NKSCC histology strongly predicts HPV-association, comparing the clinicopathological findings of our non-HPV-tested NKSCC cases and those from previously reported examples of HPV-positive NKSCCs.

Material and Methods

The files of the Surgical Pathology Service of the Hospital General de México were reviewed and all cases with diagnosis of NKSCC were selected. The protocol was approved by the Ethics Committee of the Hospital General de México "Dr. Eduardo Liceaga" and, at admission, each patient had signed a Letter of Consent. The data retrieved were: age, gender, location, treatment, TNM status, clinical stage, lymph node involvement and recurrence.

The H&E stained slides were retrieved and the El-Mofty et al. [5] classification was applied to all analyzed cases. Briefly, all three types are as follows: The KSCC is a tumor consisting entirely or diffusely of maturing squamous epithelium without NKSCC areas or basal morphology. The cells have polygonal shapes with abundant, eosinophilic, keratinizing cytoplasm; distinct cell borders, intercellular bridges, and is frequent to find marked stromal desmoplasia. Keratin formation is common but is not required, and the tumors range from well to poorly differentiated. NKSCC consists of sheets, nests, or trabeculae of oval and frequently spindled hyperchromatic cells with indistinct cell borders, absence of prominent nucleoli, and scarce amount of eosinophilic cytoplasm. Comedonecrosis and mitotic activity are frequently present with minimal stromal reaction. Portions of the tumor can show squamous maturation and keratin pearls, but these areas must comprise <10% of the total surface area. The hybrid SCC variant, also known as NKSCC with maturation is an intermediate group of SCCs consisting of areas with NKSCC morphology mixed with maturing squamous differentiation comprising >10% of the tumoral area.

These "maturing areas" are similar to those composing the KSCC. Frequently they show "reverse maturation" where the basal-appearing cells are central in the nests and the cells at the periphery show squamous maturation. TNM and staging of the analyzed cases were built according to the AJCC Cancer Staging Manual [21]. Student t-test was applied and a $p<0.05$ was considered significant.

Results

Clinicopathological features of the NKSCCs analyzed in this study are presented on Table 1. From the 30 examined cases of NKSCC, the most frequent type was the hybrid SCC (83.3%). All the tumors were moderately growing, invasive, elevated masses, firm inconsistency with ill-defined boundaries, their color varied from pink to red with white, black, or brown areas, and sometimes we detected ulcerated, painful zones. NKSCCs were more common in men (60%). Ages were between 20 and 83 years with a mean age of 56.5 years. Women's age was between 36 and 74 years, with a mean age of 55.1 years, and in men the mean age was 57.4 years. NKSCC patients were slightly younger than those diagnosed with hybrid SCC (mean age = 54.0 years and 59.0 years, respectively), no statistical significance was found ($p>0.05$).

Hybrid SCC

Of the 30 NKSCCs, 25 cases presented >10% squamous differentiation (83.3%). They were more common in men (46.7%) and their age was between 36 and 83 years (mean age was 54 years). Female age was between 36 and 74 years (mean age = 55.2 years) and in men age was between 20 and 83 years (mean was 56.6 years). No statistical significance was also found ($p>0.05$).

NKSCC

This kind of carcinoma was the least frequent (16.7%); 80% of

Table 1: Patient and disease features of the analyzed NKSCC.

	Hybrid SCC (%)	NKSCC (%)	Total (%)
Gender			
Female	11 (36.7)	1 (3.3)	12 (40.0)
Male	14 /46.7)	4 (13.3)	18 (60.0)
Age			
<21	2 (6.7)	0 (0.0)	2 (6.7)
21-30	0 (0.0)	1 (3.3)	1 (3.3)
31-40	2 (6.7)	1 (3.3)	3 (10.0)
41-50	3 (10.0)	0 (0.0)	3 (10.0)
51-60	7 (23.3)	1 (3.3)	8 (26.6)
61-70	6 (20.0)	1 (3.3)	7 (23.3)
71-80	3 (10.0)	1 (3.3)	4 (13.3)
81>	1 (3.3)	0 (0.0)	1 (3.3)
UK	1 (3.3)	0 (0.0)	1 (3.3)
Location			
Tongue	25 (83.3)	5 (16.7)	30 (100)
FM	8 (26.7)	2 (6.7)	10 (33.3)
Gingiva	1 (3.3)	1 (3.3)	2 (6.7)
SMG	6 (20.0)	1 (3.3)	7 (23.3)
Metastases	9 (30.0)	1 (3.3)	10 (33.3)
TNM			
T1N0M0	5 (16.7)	2 (6.7)	7 (23.3)
T2N0M0	10 (33.3)	1 (3.3)	11 (36.7)
T2N1M0	2 (6.7)	0 (0.0)	2 (6.7)
T3N0M0	1 (3.3)	1 (3.3)	2 (6.7)
T4N1M0	1 (3.3)	0 (0.0)	1 (3.3)
T4N2M0	6 (20.0)	1 (3.3)	7 (23.3)
Stage			
1	5 (16.7)	2 (6.7)	7 (23.3)
2	10 (33.3)	1 (3.3)	11 (36.7)
3	3 (10.0)	1 (3.3)	4 (13.3)
4	7 (23.3)	1 (3.3)	8 (26.7)
Treatment			
EB	20 (66.7)	6 (20.0)	26 (86.7)
WR	4 (13.3)	0 (0.0)	4 (13.3)
RES	2 (6.7)	0 (0.0)	2 (6.7)
Hemiglosectomy	7 (23.3)	0 (0.0)	7 (23.3)
Glossectomy	6 (20.0)	0 (0.0)	6 (20.0)
SMG Res	7 (23.3)	0 (0.0)	7 (23.3)
CLN Res	9 (30.0)	1 (3.3)	10 (33.3)
Patients with recurrence	16 (53.3)	1 (3.3)	17 (56.7)
Recurrences	20 (66.7)	1 (3.3)	22 (70.0)

them were in men and their ages varied between 35 and 78 years with a mean age of 59 years. There was one female patient, 54 years of age; the age in men was between 35 and 78 years (mean age = 60.2 years).

TNM status

Most of the tumors (66.6%) were T1-T2, followed in frequency by T4 malignancies (26.7); 56.7% of the sample was T2-hybrid SCCs, and this variant comprised 87.5% of the T4 cases. The tumors in men corresponded to 50% of the T4 group, 53.8% of the T2 neoplasms, and 16.7% of the T1 set of malignancies.

Lymph node involvement (LNI)

Of the 30 participating patients, 10 of them presented LNI (33.3%). LNI was slightly more frequent in men (60%), 80% of the implicated patients were older than 40 years. All the tumors with LNI were hybrid SCCs and they were 40% of all hybrid SCCs. All T4 cases (100%) exhibited LNI and only 11.8% of T2 malignancies developed LNI.

Staging

Patients in early stages of the disease (stages 1 and 2) corresponded to 60%, those in stage 4 were 26.7%, and individuals in stage 3 were 13.3%. Tumors in stage 2 (54.5%) were more frequently detected in women, and neoplasms in men were more commonly noticed in stage 1 (71.3%); statistical significance was encountered (p=0.03). Surprisingly, all stage 3 tumors (100%), and 50% of those in stage 4 were in men. Age of patients in stage 1 was between 36 and 78 years (mean age = 58.7 years), for stage 2 tumors it was from 40 to 70 years with a mean age of 58.5 years, patients age in the stage 3 varied from 61 to 83 years (mean age = 63.7 years). Interestingly, neoplasms in stage 4 were found at ages from 20 and 74 years, obtaining the lowest mean age (48.6 years). Statistical difference was found in the ages of patients in stage 4 ($p<0.05$).

It is important to note that the youngest patients harbored stage 4 neoplasms. The most aggressive tumors were in T-3 and T4 (33.3%), all invaded the floor of the mouth, and seven of them were seen infiltrating the submandibular salivary gland (23.3%). Additionally, two tumors, invading de floor of the mouth, extended to the gingiva (6.7%).

Microscopic features. NKSCCs corresponded to a group with distinct morphologic characteristics with basal cell-like components being the main cytological feature (Figure 1). The neoplastic cells generally bear a striking resemblance to basal cells, forming sheets, nests, trabeculae, and cords surrounded by scant fibrous connective tissue stroma (Figure 2). Microscopically, in the NKSCC variant, these neoplastic cells were monomorphic, round, oval, and spindle-shaped, showing scanty cytoplasm and ill-defined cellular limits. Their nuclei were hyperchromatic with an increased nucleus-cytoplasm ratio and inconspicuous nucleoli (Figure 3). Mitotic figures and apoptotic bodies were detected, and comedonecrosis was

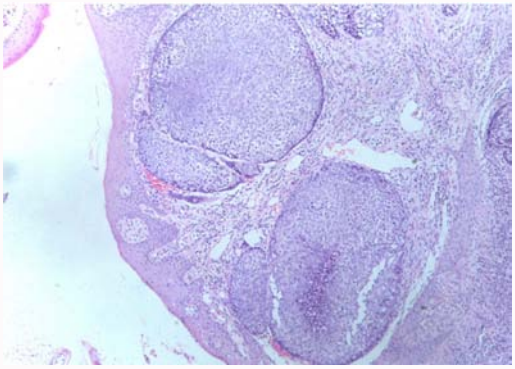

Figure 1: Histological section showing solid midi of malignant epithelial cells infiltrating the subepithelial stroma of the tongue. They are well limited by a thin pseudocapsule.

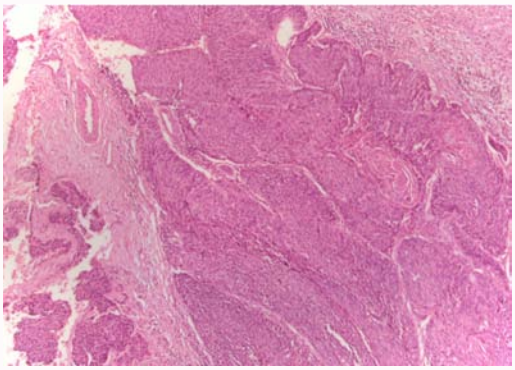

Figure 2: A solid neoplasm is observed constituted by cohesive epithelial cells with stromal infiltration. Cells have a basaloid aspect with scarce eosinophilic cytoplasm and a hyperchromatic and atypical nucleus.

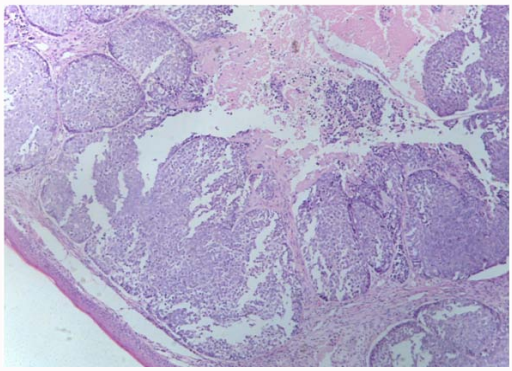

Figure 3: Comedo-type necrosis in the central part surrounded by malignant epithelial cells scarcely differentiated without keratinization.

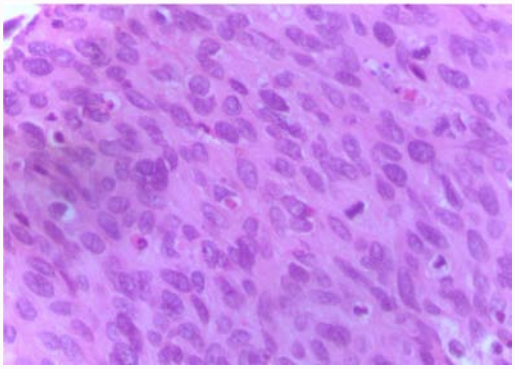

Figure 4: Close-up of the cellular detail showing atypical cells with enlarged nuclei with heterochromatin, poorly apparent nucleoli and the presence of abnormal mitosis figures.

also found. Some areas had cells approaching cellular maturation, forming individual or small groups showing keratinization; keratin pearl formation was occasionally observed and, generally, these structures were insignificant or absent. Hybrid variants of the NKSCCs were analogous to the above-described neoplasms. The difference was their higher content of areas with maturing squamous differentiation comprising >10% of the whole tumoral area (Figure 4). These "maturing areas" were similar to those found composing the conventional type of SCC.

Treatment

Surgical treatment was done in all patients (100%). Treatment modalities varied from excisional biopsy, resection of the tumor, wide resection, hemiglossectomy and total glossectomy.

Recurrence

In the 30 analyzed cases, 22 recurrences appeared in 17 patients (56.7%), occurring between 7 and 167 months after primary surgical excision (mean = 60 months).

One tumor was recurrent at first appointment in the hospital. Recurrences were more common in patients with hybrid SCCs (n=16; 94.1% of the recurrent tumors and 53.3% of all analyzed cases) than in patients with NKSCCs. The tumors recurred more frequently in men (64.7%) and were more frequent in patients older than 50 years (n=11; 64.7%). All recurrences developed in patients treated with excisional biopsy (no data on clinically free surgical margins was found).

Discussion

The NKSCC is a distinct clinicopathologic subtype of the SCC of the head and neck, it has a distinct basal cell morphology, stains diffusely and strongly with p16 antibodies, had a higher Ki 67 labeling index and a lower p53 reactivity score compared with the conventional KSCC of the head and neck [3,11,16-20,22,23]. During many years, misinterpretation of the NKSCC microscopic features with other small, basal cell-like composed malignancies of the OP occurred [21-24]. Features distinguishing NKSCC from these neoplasms are its more frequent development in younger, male patients; it is more common in the base of the tongue and palatine tonsils and apparently tobacco smoking and alcohol consumption do not appear to be important factors influencing its development [3,11,16-20,22,23].

These significant features were overlooked during a long time because when compared to the conventional KSCC, it has a monotonous microscopic appearance and superior response to treatment [21]. These features prevented its recognition as a distinct subtype of the head and neck SCC.

Epidemiological and clinicopathological data on NKSCCs developing in the tongue tissues are not available in the literature, since existing data are mixed with information from different parts of the OP. Only the El-Mofty and Patil report [20] distinguished the tonsillar tumors from the base of the tongue cases, but only age and gender of patients were reported. For this reason, results from that study were compared with data from reports of cases arising in distinct oropharyngeal subsites. From our study, the first unexpected finding was to observe that from the 30 analyzed cases, most tumors (83.3%) were hybrid SCCs. This finding is different from previously reported series, since in the NKSCCs were more common [3,14,16,18]. Agreeing with previously published reports [5,16,18-20], data from these 30 examined examples reveal that they were more commonly detected in men.

It is important to mention that the M:F rate varied greatly between our sample and the before mentioned studies. Mean age of the NKSCCs was 56.5 years and, surprisingly, it was slightly younger for male patients. Mean age for NKSCCs in this study was very similar to data previously published [16]. Likewise, mean age for NKSCCs in both genders was lower than that found in hybrid SCCs. Also, mean age in women with hybrid SCC was higher than that found in male patients.

Most analyzed tumors (66.7%) were in the early stage of malignant development (T1, T2) and one quarter was in T4. Interestingly, 56.7% of the T2 tumors were hybrid SCCS and this variant corresponded to

87.5% of the T4 cases. In contrast, no T4-NKSCC was detected and all the T1-T2 tumors were NKSCCs (100%). Only one third of the tumors developed lymph node involvement (33.3%), all of them were hybrid SCCs. These findings support data previously reported [13], suggesting that NKSCCs are less aggressive neoplasms compared with hybrid SCCs.

Interestingly, 80% of the patients developing LNI were 40 years or older. In this study, 33.3% of the hybrid SCCs and 6.6% of the NKSCCs were in stages 3 and 4, suggesting that hybrid SCCs are more aggressive malignancies. In contrast, the Chernock et al. [15] study reported that 96.7% of the NKSCCs were in stages 3 or 4 and 98.4% of the hybrid SCCs were in the same stages. Results from both studies suggest that hybrid SCCs are more aggressive than NKSCCs, but comparing both data sets, Chernock et al. [15] cases presented a more aggressive behavior. These data also confirm that NKSCCs have a better prognosis; 56.7% of the patients developed 22 recurrences and 94.1% of these recurrent tumors were hybrid SCCs, supporting the proposal that hybrid SCCs are more aggressive than the NKSCCs and assigning better prognosis to NKSCCs. Of the recurrent tumors, 64.7% occurred in men, 64.7% of them developed in patients older than 50 years, and all recurrences were in patients treated by excisional biopsy. These findings suggest that gender, age, and treatment are important factors for recurrence.

The microscopic classification is simple and relatively straightforward. It also correlates well with HPV detection by ISH and p16 immunohistochemistry [5,19,20]; as shown, the accurate identification of the non-keratinizing morphologic features in oropharyngeal squamous cell carcinomas can be used as predictor of favorable clinical outcome [16]. The non-keratinizing morphology is significantly more likely to be HPV andp16 positive than KSCC, and to have better overall survival and disease specific survival [16,17]. However, the use of the histologic classification in determining HPV association has not gained widespread acceptance. This may be, in part, due to the lack of studies that correlate histologic features directly with patient outcome [16].

Chernock et al. [15] demonstrated that for SCC with NK morphology, adjuvant testing is not necessary as 100% are p16 positive, and that HR HPV-ISH status does not appear to further stratify tumor behavior [16]. This point of view is supported by results of numerous previous studies [5,8,11-13,15,17-20]. We agree with Chernock et al. [15] viewpoint, hoping that more information to pathologists will increase familiarity with the microscopic features of NKSCCs, which might lead to the use of simple light-microscopic examination as an integral part of the algorithm for the detection of HPV-related carcinomas.

It should be taken into a count that NKSCC present similar morphology to several malignant tumors of the oropharyngeal area, such as the basaloid SCC, undifferentiated carcinoma, small cell carcinoma, poorly differentiated SCC, NK-type of papillary SCC, metastatic small cell carcinomas from the lungs and other organs [21-23], and a set of undiagnosed small cell tumors reported by Bishop and Westra [23]. These malignancies must be distinguished from NKSCC since their behavior and prognosis is different.

Results from this study strongly suggest that non-HPV tested NKSCCs displayed similar clinicopathological features and biological behavior to the HPV-positive NKSCCs. Our results support the Chernock et al. [15] conclusion that NKSCC microscopic features strongly predict HPV association.

Conclusion

1) Clinicopathological features and behavior of NKSCCs without HPV tests were similar to those previously published with HPV-positivity. 2) Hybrid SCCs were more common than NKSCCs. 3) Only hybrid SCCs developed lymph node involvement. 4) NKSCCs have a less aggressive behavior and better prognosis than hybrid SCCs. 5) In this series, hybrid SCCs were the most frequent neoplasm. 6) NKSCC microscopic features could predict HPV association.

Acknowledgement

The authors are very grateful to the medical and administrative personnel of the Hospital General de México "Eduardo Liceaga" for their support.

References

1. Sloan P, Gale N, Hunter K, Longen M, Nylander K, Reibel J, et al. Malignant surface epithelial tumors. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, editors. WHO Classification of Head and Neck Tumors. 4th Ed. IARC. Lyon. 2017:109.
2. Takata T, Slooweg PJ. Tumors of the oral cavity and mobile tongue. In: El-Naggar AK,Chan JKC, Grandis JR, Takata T, Slootweg PJ, editors. WHO Classification of Head and Neck Tumors. 4th Ed. IARC. Lyon. 2017:108.
3. Lewis Jr JS, Khan RA, Masand RP, Chernock RD, Zhang Q, Al-Naief NS, et al. Recognition of nonkeratinizing morphology in oropharyngeal squamous cell carcinoma-a prospective cohort and interobserver variability study. Histopathology. 2012;60(3):427-36.
4. Fossum CC, Chintakuntlawar AV, Price DL, Garcia JJ. Characterization of the OP: Anatomy, histology, immunology, squamous cell carcinoma and surgical resection. Histopathology. 2017;70(7):1021-9.
5. El-Mofty SK, Zhang MQ, Davila RM. Histologic identification of Human Papillomavirus (HPV)-related squamous cell carcinoma in cervical lymph nodes: A reliable predictor of the site of an occult head and neck primary carcinoma. Head Neck Pathol. 2008;2(3):163-8.
6. Barnes L, Eveson JW, Reichart P, Sidransky D. Pathology and genetics of head and neck tumours. IARC Press. Lyon; 2005.
7. Westra WH, Boy G, El-Mofty SK, Gillison M, Schwartz MR, Syrjanen S, et al. Squamous Cell Carcinoma, HPV-positive. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, editors. WHO Classification of Head and Neck Tumors. Lyon, IARC Press. 2017.
8. Suster D, Pihan G, Mackinnon A, Suster S. Poorly differentiated nonkeratinizing squamous cell carcinoma of the thymus: Clinicopathologic and molecular genetic study of 25 cases. Am J Surg Pathol. 2018;42(9):1224-36.
9. Chen R, Ding Z, Zhu L, Lu S, Yu Y. Correlation of clinicopathologic features and lung squamous cell carcinoma subtypes according to the 2015 WHO classification. Eur J Oncol. 2017;43(12):2308-14.
10. Kiliç S, Kiliç SS, Kim ES, Baredes S, Mahmoud O, Gray ST, et al. Significance of human papillomavirus positivity in sinonasal squamous cell carcinoma. Int Forum Allergy Rhinol. 2017:7(10):980-9.
11. Zhang L, Lewis IS, El-Mofty SK, Gandhi M, Chernock RD. Nonkeratinizing squamous cell carcinoma in situ of the upper aerodigestive tract: An HPV-related entity. Head Neck Pathol. 2017;11(2):152-61.
12. Afrogheh AH, Jakobiec FA, Hammon R, Grossniklaus HE, Rocco J, Lindeman NI, et al. Evaluation for high-risk HPV in squamous cell carcinomas and precursor lesions arising in the conjunctiva and lacrimal sac. Am J Surg Pathol. 2016;40:519-28.
13. Huang SH, Perez-Ordonez B, Liu FF, Waldron J, Ringash J, Irish J, et al. Atypical clinical behavior of p16 confirmed HPV related oropharyngeal squamous cell carcinoma treated with radical radiotherapy. Int J Radiat

Oncol Biol Phys. 2012;82(1):276-83.

14. Westra WH. The morphologic profile of HPV-related head and neck squamous carcinoma: Implications for diagnosis, prognosis, and clinical management. Head Neck Pathol. 2012;6(Suppl1):548-54.

15. Chernock RD, El-Mofty SK, Thorstad WL, Parvin CA, Lewis JS. HPV-related nonkeratinizing squamous cell carcinoma of the OP: Utility of microscopic features in predicting patient outcome. Head Neck Pathol. 2009;3(3):186-94.

16. El-Mofty SK. Histopathologic risk factors in oral and oropharyngeal squamous cell carcinoma variants: An update with special reference to HPV-related carcinomas. Med Oral Patol Oral Cir Bucal. 2014:19(4):e377-85.

17. Muller S, Khuri F, Kono SA, Beitler JJ, Shin DM, Saba NF. HPV positive squamous cellcarcinoma of the OP. Are we observing an unusual pattern of metastases? Head Neck Pathol. 2012;6(3):336-44.

18. El-Mofty SK, Lu DW. Prevalence of human papillomavirus type 16 DNA in squamous cell carcinoma of the palatine tonsil, and not the oral cavity, in young patients: A distinct clinicopathologic and molecular disease entity. Am J Surg Pathol. 2003;27(11):1463-70.

19. El-Mofty SK, Patil S. Human Papillomavirus (HPV)-related oropharyngeal nonkeratinizing squamous cell carcinoma: Characterization of a distinct phenotype. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;101(3):339-45.

20. Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC cancer staging manual. 7th Ed. Bangalore: Springer-Verlag. 2010.

21. Stevens TM, Bishop JA. HPV-related carcinomas of the head and neck: Morphologic features, variants, and practical considerations for the surgical pathologist. Virchows Arch. 2017:471(2):295-307.

22. El-Mofty SK. HPV-related squamous cell carcinoma variants in the head and neck. Head Neck Pathol. 2012;6(Suppl 1):55-62.

23. Bishop JA, Westra WH. Human papillomavirus-related small cell carcinoma of the oropharynx. Am J Surg Pathol. 2011;35(11):1679-84.