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Non-epithelial neoplasms of the larynx and hypopharynx – 12 – years of experience

Nienabłonkowe nowotwory krtani i krtaniowej części gardła – 12 lat doświadczeń

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:

Objective: The non-epithelial neoplasms of larynx and hypopharynx are of rare incidence but may originate from various histological tissues. These effect in the difficulty of final diagnosis and often delay the proper treatment.

Material and methods: There was performed retrospective analysis of patients with histopathologicaly confirmed non-epithelial neoplasms of larynx or hypopharynx between 2001 and 2013, that included the evaluation of epidemiology, diagnostic methods and treatment.

Results: Non-epithelial neoplasms of larynx and hypopharynx were established in 18 patients (9 women, 9 men), mean age – 60,3 years. The malignant neoplasms were diagnosed in 10 patients and benign - in 8. The soft tissue neoplasms were the most common - 8 patients. There were also 4 lymphomas, 4 chondrosarcomas, 1 paraganglioma and 1 malignant melanoma. Tumors manifested clinically as covered by unchanged mucosa. Characteristic features were observed on computed tomography for certain cases of these neoplasms. The results of the tumor biopsy were in most of the cases not diagnostic. Intralaryngeal microsurgery was applied in benign neoplasms, chemiotherapy - for lymphomas and total laryngectomy for chondrosarcomas and malignant melanoma.

KEYWORDS: larynx, non-epithelial neoplasm, larynx chondrosarcoma, larynx lymphoma, larynx soft tissue neoplasms

STRESZCZENIE:

Cele badania: Nienabłonkowe nowotwory krtani i krtaniowej części gardła są rzadko występującymi guzami, ale mogą wywodzić się z różnych typów histologicznych tkanek. Powoduje to trudności w postawieniu ostatecznej diagnozy oraz często opóźnia wdrożenie właściwej terapii.

Materiał i metody: Przeprowadzono retrospektywną analizę hospitalizowanych w latach 2001-2013 pacjentów z histopatologicznie potwierdzonymi nowotworami krtani lub krtaniowej części gardła, obejmującą analizę danych epidemiologicznych, metod diagnostycznych oraz leczenia.

Wyniki: Nienabłonkowe nowotwory krtani i krtaniowej części gardła rozpoznano u 18 pacjentów (9 kobiet, 9 mężczyzn), średni wiek postawienia diagnozy wyniósł 60,3 lat. Z tego nowotwory złośliwe występowały u 10 pacjentów, a łagodne - u 8. Najczęściej występowały nowotwory tkanek miękkich - 8 pacjentów. Oprócz tego rozpoznano 4 chłoniaki, 4 chrzęstniakomięsaki, 1 przyzwojaka i 1 czerniaka złośliwego. Klinicznie guzy manifestowały się jako zmiany pokryte niezmienioną błoną śluzową. W niektórych przypadkach tych nowotworów obserwowano charakterystyczne cechy w badaniu TK. Wyniki biopsji guza były w większości przypadków niediagnostyczne. W przypadku nowotworów łagodnych stosowano zabiegi mikrochirurgii wewnątrzkrtaniowej, chłoniaków - chemioterapię, a chrzęstniakomięsaków i czerniaka złośliwego - całkowitą laryngektomię.

SŁOWA KLUCZOWE: krtań, nowotwór nienabłonkowy, chrzęstniakomięsak krtani, chłoniak krtani, nowotwory tkanek miękkich krtani

INTRODUCTION

The majority (90-95%) of neoplasms located in the larynx and hypopharynx originate from the epithelium. However, histological differentiation of anatomical structures of these organs enables growth of neoplasms derived from nearly all tissues: connective tissue, muscles, cartilage, vascular, lymphatic or neural. These non-epithelial neoplasms (NEN) are rarely encountered in laryngological practice, but they surely must be taken into consideration in the differential diagnosis of head and neck tumors. Otherwise the diagnostic process and the treatment procedures can be significantly delayed.

MATERIALS AND METHODS

We conducted a retrospective analysis of medical documentation of patients with the diagnosis of non-epithelial neoplasms of the larynx and/or hypopharynx, that was confirmed by histopathological examination. Patients were hospitalized in our Department of Otolaryngology in the period from 2001 to 2013. We evaluated:

- the epidemiological and clinical data
- the usefulness of additional investigations: X-rays, biopsy and histopathology in establishing the final diagnosis
- the performed treatment
- The study was approved by the Bioethics Committee of the local Medical University.

RESULTS

The non–epithelial neoplasms of the larynx and/or hypopharynx were diagnosed in 18 patients (9 women and 9 men), mean age 60.3 years, during the period of 12 years. The malignant neoplasms slightly predominated - 10 cases (55.6%) and the mean age in that group was 68.2. The group of patients with benign tumors was on the other hand younger, with a mean age of 50.5 years. For both malignant and benign non-epithelial neoplasms the period from the onset of symptoms to hospitalization was quite long, i.e. over a half of the year.

In our material the most commonly diagnosed non-epithelial neoplasms of the larynx and/or hypopharynx were the soft tissue neoplasms – 8 cases, which were mostly benign tumors. The lymphomas were detected in 4 patients. There were also 4 cases of chondrosarcomas and one case of laryngeal paraganglioma and malignant melanoma. Considering different histopathological types of the diagnosed non-epithelial neoplasms and their location in the larynx and/or hypopharynx we found that for soft tissue neoplasms the dominating location were the vocal and ventricular folds, whereas chondrosarcomas, in majority low grade – G1, occupied the subglottic area. Lymphomas, two of which were mucosa-associated lymphoid tissue lymphomas (MALT) and the remaining two: diffuse large B-cell lymphoma (DLBCL) and plasmacytoma invaded the supraglottic structures. Only two cases of non-epithelial neoplasms were limited to the hypopharynx: MALT lymphoma and fibrolipoma. There is a detailed presentation of histopathological types of all diagnosed non-epithelial neoplasms and their location in the larynx and/or hypopharynx in Table 1.

The symptoms reported on examination were not characteristic and the patients complained of the following disorders:

- chronic hoarseness (soft tissue neoplasms – 7)
- dysphagia (fibrolipoma, MALT lymphoma)
- dyspnoe (lymphomas – 2)
- blood in sputum (paraganglioma)
- On direct laryngoscopy the non-epithelial neoplasms presented as:
- small lesions on vocal folds with external growth, very similar to granuloma (granular cell tumor, fibroma, neurofibroma)
- well-bordered tumors covered with normal mucosa (neurofibroma, chondrosarcoma)
- small, reddish and congested tumors of the vocal fold (haemangioma, malignant fibrohistiocytoma - MFH)
- thickening of the laryngeal mucosa (lymphoma)
- hemiparesis of the larynx (in all cases of chondrosarcoma)

The radiological examination of the tumor was performed in cases of lymphomas, chondrosarcomas and paraganglioma. On computed tomography (CT) scans of laryngeal lymphomas there were no specific features that would enable the radiologists differentiate them from malignant epithelial neoplasms.

However, CT scans of chondrosarcomas were more significant and in all cases there were typical for these tumors calcifications, as well as the destruction of the cricoid cartilage.

In case of laryngeal paraganglioma the CT scan revealed a very well vascularized tumor with the leading blood vessel deriving from the upper thyroid artery.

As concerns the significance of the biopsy that was performed during the direct laryngoscopy: it was accurate in setting the final diagnosis of non-epithelial neoplasms only when followed by a routine histopathological examination with paraffin

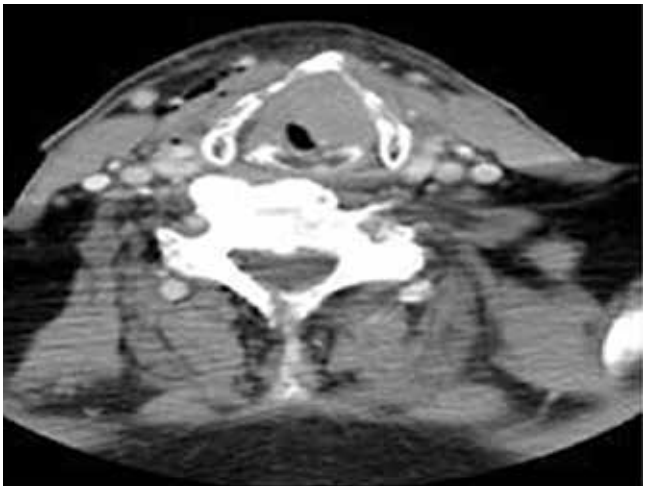

Fig. 1. CT scan of laryngeal DLBCL.

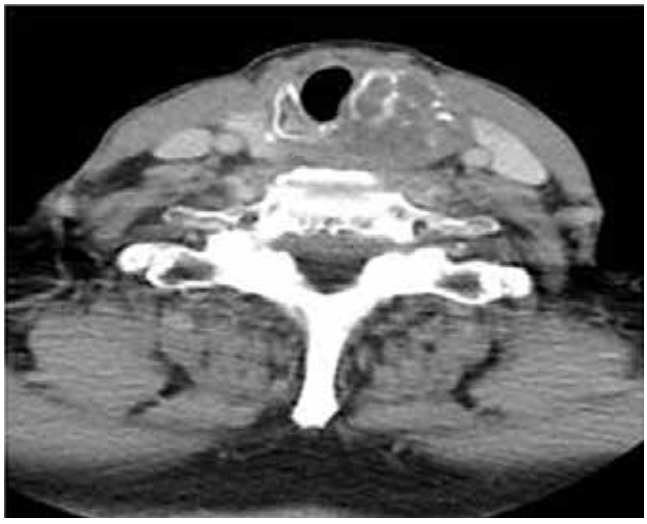

Fig. 2. Destruction of the cricoid cartilage and calcification in the mass of laryngeal chondrosarcoma.

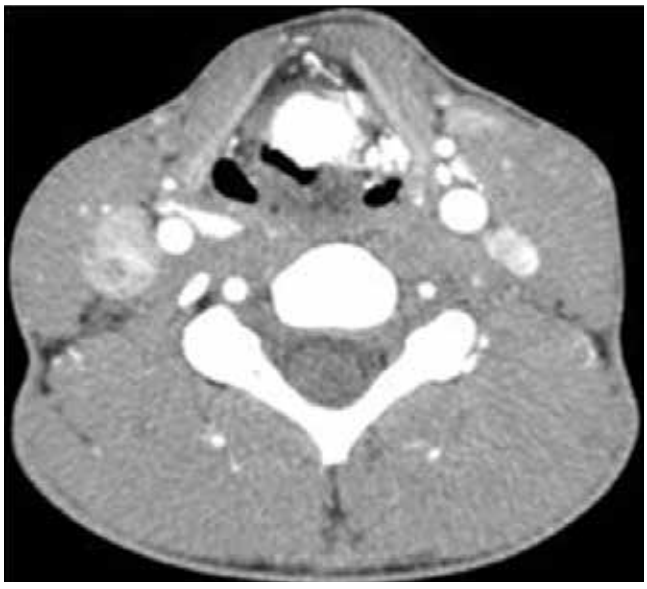

Fig. 3. Intensive enhancement of laryngeal paraganglioma on CT.

blocks (Table 2). Out of 9 biopsies performed in this way, 7 were diagnostic (lymphomas in 4 cases, chondrosarcoma in 2 cases and one case of MFH). In cases of melanoma malignum the histopathological exam confirmed only malignant neoplasm, but for paraganglioma it was not diagnostic. The intraoperative biopsy followed by histopatological examination of frozen specimens was false negative in all performed cases: one of neurofibroma and two cases of chondrosarcoma (where it suggested the diagnosis of chondroma, which was the reason for a delay in the final, radical resection of the malignant neoplasms).

Patients with non-epithelial neoplasm of the larynx and/or hypopharynx were treated surgically in the majority of cases. Different procedures were applied concerning the type, size and location of the pathology and they were all presented in Table 3.

The emergency tracheotomy had to be performed in two patients with lymphoma of the larynx. All patients with lymphomas of the larynx and/or hypopharynx were directed to the Hematology Department for chemo- and radiotherapy.

The follow-up was available for 12 patients, including all cases of benign NEN (Table 4). The mean time of observation was 26.9 months and there was no evidence of recurrence in any of the cases.

Unfortunately, the majority of patients with laryngeal lymphomas directed for further hematological therapy did not appear for a control follow-up in our department. For the rest of malignant neoplasms the mean time of follow-up was nearly 40 months, with no evidence of local recurrence. Three patients with malignant NEN died during the observation, but only the patient with MALT lymphoma died because of the disease progression. Death of two patients with chondrosarcomas was caused by other systemic diseases.

DISCUSSION

Non-epithelial neoplasms, both malignant and benign, are very rare in the area of the larynx and hypopharynx. In the literature, most of the papers are case reports or they concern

only one type of these neoplasms. We concluded that an analysis of all these neoplasms together could be quite useful for comparative diagnosis.

Primary laryngeal lymphomas account for less than 1% of neoplasms of this organ [1]. More frequently, lymphomas infiltrate the larynx or pharynx secondly to the neck lymph node or thyroid lymphomas [2]. According to other authors, the most commonly diagnosed lymphomas in the larynx are MALT lymphoma, DLBCL lymphoma and extramedullary plasmacytoma and they are located mainly in the supraglottic area of the larynx [1,2]. Chan et al. claims that most of the laryngeal lymphomas (>90%) are low-grade IE or IIE according to the Ann Arbor scale [2].

Chondrosarcoma is the most common sarcoma recognized in the larynx [3,4]. Some authors claim that these neoplasms predominate in males usually over 50 years old [3,4].

The symptomathology of non-epithelial neoplasms in the larynx and hypoharyx is not different from other laryngeal tumors. On examination, the non-epithelial neoplasms present as thickening of the mucosa or tumors covered with normal mucosa. The ulceration was not present in any of our patients.

Granular cell tumors and fibromas, that are frequently located on the vocal folds, are very similar to granulomas. However, the last one occupies mostly the posterior region of the glottis due to the injury origin [5]. The neuroma and neurofibroma of the larynx are usually well bordered, round or oval submucosal tumors and predominantly occur in the aryepiglottic fold or ventricular fold according to the location of the superior laryngeal nerve, whose sheath is the origin for these tumors [6,7]. Neurofibromas in the subglottic area are described extremely rarely and they presumably derive from recurrent laryngeal nerve.

Straetmans et al. presented two cases of plasmacytoma that manifested at first as subglottic stenosis [8]. Vegas et al. described the plasmacytoma as a polypus tumor of the epiglottis [1]. In case of extramedullary plasmacytoma there is the necessity of additional blood sample and bone marrow examination to exclude multiple myeloma, as the treatment methods in both cases are different [4,8]. Also, sarcomas of the larynx are described in the literature as tumors covered by unchanged mucosa which may differentiate them from epithelial carcinomas [4,9]. Lewis et al. reported that chondrosarcoma may present at first as a neck tumor, when the growth spreads externally out of the thyroid cartilage [4]. The same author claimed also that most of the laryngeal chondrosarcomas present with laryngeal paresis and destruction of the cricoid cartilage. The same was

Tab. I. Localization of different types of non-epithelial neoplasms in larynx and/or hypopharynx.

THE HISTOPATHOLOGICAL TYPE OF NEN	NUMBER OF CASES	LOCALISATION IN LARYNX AND /OR HYPOPHARYNX
Soft tissue neoplasms:	8	
Haemangioma	1	vocal fold
Fibroma	1	vocal fold
Neurofibroma	2	ventricular fold
Fibrolipoma	1	piriformis sinus
Granular cell tumor	2	vocal fold,
Malignant fibrohistiocytoma (MFH)	1	ventricular fold vocal fold
Cartilage neoplasms:	4	
Chondrosarcoma G1	3	subglottic area (2), thee levels of larynx and thyroid gland (1)
Chondrosarcoma G2	1	subglottic area (1)
Lymphomas:	4	
MALT	2	piriformis sinus, aryepiglottic fold
DLBCL	1	epiglottic and
Plasmacytoma	1	glottis area aryepiglottic fold
Paraganglioma	1	aryepiglottic fold
Malignant melanoma	1	ventricular fold, Morgani's ventricle

believed about chondrosarcomas, i.e. that they can arise from benign chondromas. However, according to the new criteria of histopathological diagnosis of chondroma, this diagnosis is reserved for small tumors under 1-2 cm of diameter, that were excised totally and entirely examined histopathologically [4]. Lewis et al. suggested that earlier most of the low-grade chondrosarcomas had been incorrectly diagnosed as chondromas. Fortunately most of the laryngeal chondrosarcomas, even 90%, are well differentiated G1 or G2, compared to other locations of these tumors [3,4]. Distant metastases are described in 10% of chondrosarcomas and the lungs are usually the first place of the spread.

For paraganglioma the laryngeal location is the rarest in the neck, with 70 documented cases in the literature [10,11]. Most of the described laryngeal paraganglimas were placed submucosally in the epiglottic area and they manifested as sore throat, hoarseness, hemoptysis or difficulties with breathing [12].

Mucosal malignant melanoma of the larynx is also uniquely rare, with 46 documented cases in the literature so far [13]. Terada et al. analyzed 36 cases described in the literature and concluded that 80% of laryngeal melanomas presented in males aged between 35 and 86 years [14]. In the same analysis the most common location for melanoma was the epiglottic area – 60% of cases - and less frequently the tumor invaded

Tab. II. Comparison of the results of an intraoperative and routine histopathological examination after biopsy of non-epithelial laryngeal neoplasms.

THE TYPE OF THE BIOPSY	NUMBER OF BIOPSIES	POSITIVE DIAGNOSIS	NEGATIVE DIAGNOSIS
Biopsy followed by routine histopathological examination	9	7 (lymphomas-4, chondrosarcomas-2, MFH)	2 (melanoma, paraganglioma)
Intraoperative biopsy	3	0	3 (neurofibroma, chondrosarcoma-2)

Tab. III. Methods of performed surgical treatment in patients with non-epithelial neoplasms of the larynx and/or hypopharynx.

SURGICAL TREATMENT	TYPE OF NEOPLASMS (NUMBER OF CASES)	COMPLICATIONS
Directoscopy with biopsy	lymphomas (4)	No
Emergency tracheostomy	lymphomas (2)	No
Microsurgery conventional	GCT (2), fibroma (1), neurofibroma(1), fibrolipoma(1).	No
Microsurgery with CO_2 laser	Haemangioma (1), MFH (1)	No
Laryngeal fission with transient tracheostomy	neurofibroma (1), paraganglioma (1)	No
Total laryngectomy	chondrosarcoma (1), melanoma malignum (1).	No
Total laryngectomy with partial resection of thyroid gland	chondrosarcoma (3)	No

vocal folds or the posterior commissure [14]. Wenig et al., on the basis of 4 cases, described the macroscopic features of laryngeal melanoma as pediculed or polypoid tumors, whitish-grey or reddish-blue in color, of the maximal size of 3 cm in diameter [13].

Considering the radiological diagnosis of non-epitelial tumors according to other authors and our observations, some features on CT scans can be helpful in differing them from epithelial malignancies. According to Vega et al. lymphomas in the larynx are more homogenous and better separated than epithelial cancers, which usually infiltrate surrounding tissues [1]. None of our patients with laryngeal lymphomas presented with paresis of vocal folds or cartilage destruction. On the contrary, chondrosarcomas of the larynx on CT scans are usually well bordered tumors of low density with calcifications and causing the destruction of the cartilage [4]. Magnetic resonance (MR) imagining of chondrosarcomas could be helpful in precise evaluation of tumor borders. However the calcifications may not be seen [4]. The neuromas and neurofibromas present on CT as well bordered tumors with a hypodense area in the central part. MR imagining is more precise in this type of tumors and in T2 option they are hyper-intensive peripherally, while in the central part the intensity is intermediate, which may resemble the image of the target [7]. Paraganglioma on CT scans will highly enhance after contrast administration and on angio-CT it is possible to define the main supplying artery of the tumor, characteristic for paragangliomas [15].

Most of the authors agree that benign non-epithelial neoplasms should be excised surgically with the preservation of laryngeal functions, preferably with microsurgical endolaryngeal methods, although extralaryngeal approaches are accepted and indicated in some cases.

Tab. IV. The follow-up results in patients with non-epithelial neoplasms of the larynx

NON- EPITHELIAL NEOPLASMS	NUMBER OF PATIENTS (%)	MEAN TIME OF FOLLOW-UP (MONTHS)	RECURRENCE
Total	12 (66.7%)	31.1	No
Malignant	4 (40%)	39.5	No
Benign	8 (100%)	26.9	No
Deaths	3 (16.7%)	45	1 yes/2 no

For the granular cell tumor (GCTs) the entire tumor resection is recommended; otherwise there are local recurrences, found in 8-21% of cases [5]. Small GCTs (under 2 cm) should be resected endoscopically with laser or classic methods. GCTs larger than 4 cm, showing intensive grow or recurrence should be suspected of malignant character, which is described in 1-3% of these tumors [5,16]. The treatment option for neuromas and neurofibromas depends on the size of the tumor and its location in the larynx. For large tumors external approaches are recommended, including laryngeal fission, lateral faryngotomy or lateral tyreotomy with or without temporal tracheotomy [7].

There is general agreement that soft tissue sarcomas should be excised with wide margins of healthy tissue. However, there are no conclusions concerning the size of these margins in head and neck sarcomas [17]. Lymphadenectomy is not

recommended routinely in these toumors, because of rare lymph node metastases. However, each patient with laryngeal sarcoma should undergo chest X-ray or even CT to exclude lung metastases. Koch et al. reported on surgical resection of laryngeal chondrosarcoma in 78 out of 89 cases (87.6%) [3]. In his material, local tumor resection was performed in 21.8%, partial laryngectomy in 11.5%, total laryngectomy in 53.8% and laser microsurgery in only 10 cases. In that group of patients the 5-year survival was 88% and regional metastases were described in 56%, while the distant in 6.7% of cases [3]. The authors suggest that total laryngectomy is probably the most reasonable method to avoid local reoccurrence and lung metastasis [3].

The treatment of choice for lymphomas is chemo- and radiotherapy. Laryngoscopy is performed to establish the advancement of tumor in the larynx and especially to take biopsy for histopathological diagnosis. However, in cases with intense difficulty in breathing, tracheotomy should be prformed before oncological treatment. An exception among laryngeal lymphomas constitutes plasmacytoma, which can be resected surgically or treated with radiotherapy with comparable results [8,15,16]. Some authors described laser surgery as an effective method of plasmacytoma treatment. However, in 20-30% of patients with extramedullar pasmacytoma, multiple myeloma is diagnosed during observation [18]. In our material, the patient with plasmacytoma was treated because of multiple myeloma two years earlier, so the plasmacytoma in the larynx was secondary to the primary disease and chemotherapy was administered.

All 46 cases of laryngeal paragangliomas described in the literature after 1972 were treated surgically and the most frequently performed approach was through the laryngeal fissure, endoscopic microsurgery and lateral faryngotomy [12].

Mucosal melanoma is one of the most malignant neoplasms and its prognosis is very poor. The treatment method is radical surgery and for laryngeal location - total laryngectomy with or without lymphadenectomy. Wenig et al. in his material reported on total laryngectomy in all 4 patients, with additional radiotherapy in 3 cases. However, metastases were diagnosed in 3 patients during the 3-year period and they were the cause of death [13]. Terada et al. analyzed treatment of 36 cases presented in the literature: surgery was applied in over 72% [14]. In that group, total laryngectomy was performed in 33.3%, partial – in 14% and local excision in 22%; in the remaining 17% of cases radiotherapy was conducted. Lymph node metastases were described in 65.5% of cases and distant metastases in nearly 60%. In the same analysis the authors found the 3- and 5-year survival rate in 28.6% and 7.1% of patients, respectively [14].

SUMMARY

Although the incidence of non-epithelial neoplasms in the larynx and hypopharynx is very rare, they surely must be taken into consideration in the diagnostic process. These neoplasms mostly develop submucosally and usually the mucosa is normal on clinical examination, which leads to a high percentage of negative results of biopsies of non-epithelial neoplasms. In these circumstances deep biopsy should be performed. Non-epithelial neoplasms of the larynx, especially paragangliomas and chondrosarcomas, also reveal specific features on radiological images.

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