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HISTORICAL PERSPECTIVES IN PATHOLOGY

Laryngeal Dysplasia: Persisting Dilemmas, Disagreements and Unsolved Problems—A Short Review

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Abstract

We present the historical review and current state of the histopathological classifications and terminology of laryngeal precursor lesions. Attention to recent genetic findings is also presented; although in need of additional confirmation, these raise possibility for early detection of patients at risk of dysplasia progression. Although a number of identified genetic alterations with a promising diagnostic and prognostic value are emerging, none of the known genetic alterations can be currently implemented in clinical practice as a completely reliable diagnostic and/or prognostic marker. Regarding the terminology of precursor lesions, dysplasia remains the most frequently used term, but squamous intraepithelial lesion can be used as a synonym as well. Histological findings, in spite of certain degree of subjectivity, remain at present the most reliable method for an accurate diagnosis. The current 2017 WHO classification seems to successfully stratify risk of malignant progression, with a significantly different risk of malignant progression between low-grade dysplasia and high-grade dysplasia. In case of pronounced architectural disorders, severe cellular and nuclear atypias, and an increased number of mitoses, also atypical form, the high-grade dysplasia and carcinoma in situ can be separated. The Slovenian tertiary centers have a policy of surgical removal of high-grade SILs and life-long close follow-up. Radiotherapy is reserved for more pronounced intraepithelial lesions classified as carcinoma in situ and invasive cancer. Such a distinction can facilitate clinical decision to use radiotherapy if complete surgical removal is not possible.

Keywords Laryngeal dysplasia · Review of classifications · Recent genetic changes

Introduction

Laryngeal precursor lesions, conventionally referred to as dysplasia, posed significant problems over decades among pathologists and clinicians. Disagreements, reflected on an inconsistent terminology, were centred on defining and establishing in turn histopathological criteria for distinguishing/classifying groups of clinical significance. Obviously, controversies in histopathological distinction and terminology confused clinicians, affected patients' treatment, and consequently caused the hardly comparable results of various follow-up studies [1–5]. In this short review, we revisit the evolution of the histopathological criteria and terminology of laryngeal precursor lesions and draw attention to recent genetic findings, which raise possibility for early detection of patients at risk of dysplasia progression [6–9].

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Historical Review and Current State

The first two attempts to morphologically classify laryngeal precursor lesion, were proposed by Kleinsasser in [10], and Kambič and Lenart in [11]. The former grading system, based on nuclear atypia, proposed three grades, dividing epithelial changes into simple, squamous epithelial hyperplasia, epithelial hyperplasia with occasional atypia, and carcinoma in situ wide [10]. The latter comprised a four-tier system, including the terminology: simple-, abnormal- and atypical hyperplasia, and carcinoma in situ. However, both efforts did not enjoy wider acceptance world-wide [11]. Later, classifications of laryngeal precursor lesions mirrored the terminology of dysplasia used for squamous epithelial lesions of the uterine cervix. While the potential malignant character of dysplastic epithelial changes of the uterine cervix were recognised in 1953 [12], the concept of laryngeal dysplasia was generally not accepted until 1974 at the Centennial Conference on Laryngeal Cancer [13, 14]. The same concept was later endorsed by the 1st edition of the World Health Organization (WHO) Classification "Histological Typing of Upper Respiratory Tract Tumours" in 1978 [15], as well as in its 2nd edition. The WHO classification distinguished among mild-, moderate- and severe dysplasia, while carcinoma in situ was treated separately [16]. Parallel to the evolution of the system of dysplasia in the larynx [17, 18], the term dysplasia was slowly replaced in the gynaecological pathology. In 1969, the three-tier system of cervical intraepithelial neoplasia (CIN) was introduced [19], and later the two-tier system of squamous intraepithelial lesions (SILs) was accepted. The latter was also used for the lower anogenital, squamous human papillomavirus (HPV)-associated lesions [20].

Laryngeal precursor lesions were also affected by similar terminological changes at the end of the millennium. First, in 1976 Friedmann and Osborn used the term squamous intraepithelial neoplasia (SIN) [21], and 10 years later Crissman and Fu introduced intraepithelial neoplasia of the larynx [22]. Additionally, Friedmann and Ferlito proposed the unifying scheme of laryngeal intraepithelial neopla*sia* (LIN), in which LIN I was the equivalent to mild dysplasia, LIN II to moderate dysplasia, and LIN III to severe dysplasia and carcinoma in situ [23, 24]. These attempts to directly extrapolate the morphological criteria and terminology of precursor lesions from the uterine cervix to the larynx did not prove well-founded due to different morphologic characteristics and etiological factors in the laryngeal squamous epithelium and in the uterine squamous-columnar junction [25].

Due to the inability to harmonize various new concepts on laryngeal carcinogenesis and to multiple classification systems with inconsistent terminology, the 3rd edition of WHO classification, published in 2005, presented three most frequently used systems: (1) the five -tier dysplasia system, including squamous cell hyperplasia, mild-, moderate- and severe dysplasia, and carcinoma in situ; (2) the three-tier system of squamous intraepithelial neoplasia (SIN); (3) the four-tier Ljubljana classification, which included squamous hyperplasia, basal/parabasal hyperplasia, atypical hyperplasia, and carcinoma in situ [26]. However, the three listed classifications did not solve the problems. In the interobserver variability studies, in which pathologists used all three classifications, no significant advantage was found for any of the applied grading systems and interobserver agreements among pathologists were not encouraging [27–29].

Despite a certain degree of subjectivity, histological grading of precursor lesions in the upper aerodigestive tract has remained the most important prognostic factor to predict the biological behaviour of disease and to guide clinicians in selecting appropriate treatment. In contrast to oral potential malignant disorders (OPMD), different macroscopic features of laryngeal dysplasia appear such as leukoplakia, erythroleukoplakia or mixed erythroleukoplakia as localized or diffuse lesions or flat to exophytic or papillary changes, can mimic squamous cell carcinoma (SCC) and are not directly related to morphological changes. Therefore, histologic evaluation is mandatory for diagnosis [30]. The recent 2017 WHO classification, based on morphological criteria of the amended Ljubljana classification [4], tried to harmonize the various concepts of the listed classifications and, consequently suggested a unified, two-grade system with clear morphological criteria: low-grade (LG) to include squamous hyperplasia and mild dysplasia and high grade (HG) to include moderate and severe dysplasia and carcinoma in situ. If a three-tier system is preferred, the HG dysplasia and carcinoma in situ can be separated for treatment purposes [31]. The diagnosis carcinoma in situ is reserved for rare cases with pronounced architectural disorders with complete loss of stratification and polarity and/or severe cellular and nuclear atypia, and an increased number of mitoses, also atypical forms. Such a distinction can facilitate clinical decision to use a radiotherapy if complete surgical removal is not possible [4, 31, 32]. All details of the morphological criteria for grading of laryngeal precursor lesions are presented in Chapter 3, Table 3.02 of the WHO Classification of Head and Neck Tumours [31]. The two-tier grading (low-grade vs high-grade) system was also recommended for oesophageal squamous dysplasia in the current WHO Classification of Digestive system tumours [33], and for oral epithelial dysplasia (OED)n the current WHO classification of the Head and Neck Tumours. However, the official WHO dysplasia system of the oral cavity is still divided into three grades of severity: mild-, moderate-, and severe dysplasia [34]. All

details of the morphological criteria for grading of OED are presented in the Chapter 4, Table 4.03 of the WHO Classification of Head and Neck Tumours [34].

In addition, Wenig reviewed partially adopted morphological criteria for dysplasia system in comparison with the 2017 WHO classification. He subdivided dysplasia of the upper aerodigestive tract into classic or non-keratinizing, basal-cell type, and keratinizing (differentiated), spinous-cell type [5, 30]. The former is usually without surface keratinization, with no prominent intercellular bridges, without cytoplasmic eosinophilia, and cells oriented perpendicularly to the basement membrane. The latter usually shows surface keratinization, with prominent intercellular bridges, and an increased cytoplasmic eosinophilia [4, 5]. Architectural and cytomorphological changes of epithelial cells at the basal layer are decisive for grading, while surface keratinization, epithelial maturation and thickness of epithelial abnormalities are not so significant. Dyskeratotic cells, when occurring in increased numbers throughout the entire epithelium, represent an important clue to the presence of significant dysplasia although dyskeratotic cells on their own are not definitively diagnostic for dysplasia and can be identified in non-dysplastic epithelial proliferations. The two/three-tier grading for laryngeal dysplasia is applicable for both, keratinizing and non-keratinizing dysplasia [5, 30]. According to our experiences both subtypes are frequently present in one and the same specimen, while a pure laryngeal keratinizing dysplasia predominates over non-keratinizing one. It should be additionally mentioned that rare cases of HPV-related carcinoma in situ have been reported in association with non-keratinizing histologic morphology [5].

The largest published retrospective study of laryngeal precursor lesions, graded by the amended Ljubljana classification, revealed a significant difference in progression to malignancy between LG- (1.6%) and HG-lesions (12%) without differentiation into keratinizing and non-keratinizing types of lesions. These data have strengthened the prognostic value of the modified Ljubljana classification, and consequently of the 2017 WHO classification [4]. However, also the 2017 WHO classification has not been widely accepted and is considered a stumbling block and a source of disunity with regard to the number of grades and morphological criteria [35, 36]. In attempting to understand critical aspects that could influence the great variability of malignant transformation in different grades of laryngeal precursor lesions, it is necessary to consider variations in methodologies used in the studies, such as the number of patients included, mode of treatment, persistent risk factors in patients' lives (smoking and alcohol abuse), as well as variations in the interpretation of histological grades, and duration of follow-up. These statements are supported by the multicentric study and meta-analysis of risk and interval to malignancy of patients with laryngeal dysplasia. Overall malignant transformation rate was 14%, 10.6% in mild/moderate dysplasia and 30.4% in severe dysplasia/carcinoma in situ [37]. Notwithstanding all these limitations, the 2017 WHO classification as a pure morphological system, seems applicable to routine work without onerous efforts. In a view of possible correlation with clinical behaviour/progression to malignancy (i.e., squamous cell carcinoma), it is suggested that head and neck pathologists should try to use routinely the 2017 WHO classification of laryngeal precursor lesions daily. A useful compromise is proposed, at least until controversies are resolved, if laryngeal precursor lesions are graded according to the new system. It is accepted that this may confuse some clinicians, but clarification can be made during the Multidisciplinary Head and Neck Team Meetings, and such compromise would enable further studies addressing inter-observer agreement, clinical correlations, etc.

Dysplasia, as the most widely used term to refer to precursor lesions, has been kept in the current WHO classification, with the suggested synonyms squamous intraepithelial lesions and squamous intraepithelial neoplasia. One can raise a question as to whether neoplasia, used in its strict meaning, is suitable for laryngeal precursor lesions as many of these lesions are reversible and never progress to invasive carcinoma [2]. By definition, neoplasia means a new growth, defined as a disorder of cell growth that is triggered by a series of acquired mutations affecting a single cell and its clonal progeny. The causative mutations give the neoplastic cells a survival and growth advantage, resulting in an excessive proliferation that is independent of physiologic growth signals, and therefore autonomous [38]. According to this definition, the term neoplasia seems inappropriate for laryngeal precursor lesions. In spite of these arguments both LIN and SIN were and are still used by different authors [39–43]. Trying to avoid this terminological contradiction, the term squamous intraepithelial lesions (SILs) has been introduced in laryngeal pathology. This term is less restrictive and allows for the inclusion of a wider spectrum of intraepithelial changes, ranging from squamous hyperplasia to carcinoma in situ. In their evolution, some cases of SILs are self-limiting and reversible, some persist, and some progress to SCC in spite of careful follow-up and treatment [4, 44, 45]. Within the definition of SILs, all biological possibilities are included, and the prefixes low- and high-grade SILs lead clinicians to select the most appropriate treatment. A consensus statement presented by laryngologists and pathologists on the diagnosis and treatment of laryngeal dysplasia in 2010 recommended complete excision of most lesions [46]. To define the surgical margin precisely, the endoscopic method of narrow band imaging can be used as a highly specific and sensitive technique for distinguishing non-malignant from malignant lesions [4]. Radiotherapy could be considered as an option approved by multidisciplinary team and discussed with patients [46]. In addition, the Slovenian tertiary

centers have a policy that radiotherapy is reserved for more severe intraepithelial lesions classified as carcinoma in situ and invasive cancer [4]. Particularly for case of carcinoma in situ, an incomplete surgical removal must be followed by a more radical intervention. Therefore, a distinction between severe dysplasia and carcinoma in situ can facilitate clinical decision of a selected therapy [4, 44, 45].

Recent Genetic Findings

An unsolved issue in laryngeal cancer development remains a complete spectrum of genetic changes during the process of carcinogenesis. A solution of this enigma, complemented with corresponding morphologic types of epithelial changes could lead to reliable prognostic groups and facilitate clinical decision on treatment options [45]. Most laryngeal cancers are caused by classical risk factors, such as smoking and alcohol abuse. Less than 10% of laryngeal SCCs are caused by high-risk, biologically active-HPVs [47]. In 2015, The Cancer Genomic Atlas consortium revealed that the head and neck SCC development can be divided into three genetic subgroups: SCC with transforming active HPVs (HPV+), SCC that are HPV negative (HPV-) but characterized by many mutations and numerous chromosomal gains and losses, and HPV-SCC with copy number alterations (CNA)-silent profiles, displaying only specific mutational profiles [6, 9]. The pathogenetic mechanism of HPV-related carcinogenesis has been discovered and well-investigated by zur Hausen in the uterine cervix [48]. Transforming infection inactivates *RB* and *p53* genes by E7 and E6 oncoproteins, respectively. These events result in disruption of cell cycle regulation and inhibition of *p53*-mediated apoptotic events, leading to immortalization and accumulation of genetic and epigenetic changes, required for malignant alterations. One of these events involves also oncogenic activation of the PI3K pathway [9]. Deregulation of the cell cycle by abrogation of the *RB* and *p53* pathways may occur at the beginning in all head and neck SCC, except in CNA silent tumours, in which the aetiological factors remain unknown, only aging supposed to be the risk factor. In the group of HPV- CNA-high SCCs, Leemans et al. described many genes and pathways presumptively involved in malignant progression. The authors specially exposed among them *FAT1* and *NOTCH1,* which may act in the *WNT-β* catenin pathway, and smoking as the leading risk factor [9].

Regarding HPV-related laryngeal SCC, only a few studies of laryngeal precursor lesions have to date addressed to this topic. The overall prevalence of HPV related lesions in six studies, detected by different methodologies, published since 2005, was 8.5% ranging from 0 to 38.5% [49]. Gale et al. detected transcriptionally active HPV in only 2 of 57 patients with laryngeal SILs, and invasive SCC, however, the concomitant history of many years smoking additionally clouded the role of HPV infection in laryngeal carcinogenesis in these two HPV positive cases [50]. Zhang et al. described the transcriptionally active HPV infection in 10 cases, the dysplastic lesions appeared most commonly in the floor of mouth, but the larynx was also involved in three of ten cases. These authors are of opinion that non-keratinizing morphology is a strong predictor of transcriptionally-active HPV in severe dysplasia/carcinoma in situ. [51].

Approaches attempting to differentiate between progressing and non-progressing laryngeal precursor lesions are certainly appealing. If established and combined with conventional histopathological assessment, they could create prognostic groups and facilitate decision/improve management [49]. In a case–control study, Manterola et al. showed a comparison of genetic changes in non-progressing and progressing laryngeal dysplasia. The study revealed that mutations in *FGFR3* and *PIK3CA* genes were present in progressing lesions and laryngeal cancers but were absent in non-progressing laryngeal dysplasia. On the other hand, mutations in *JAK3, MET, and FBXW7* genes were found in non-progressing lesions, but not in progressing lesions or invasive SCC. *p53* gene was the most frequently mutated gene in both progressing and non-progressing cases of dysplasia [8]. Notwithstanding, the prognostic value of these molecular alterations needs further studies before their implementation to routine clinical practice. Rodrigo et al. explored the role of NANOG, a master regulator of embryonic stem cells pluripotency, in the process of laryngeal cancer development. Immunohistochemically, a strong cytoplasmic expression of NANOG (intense and homogenous cytoplasmic staining in dysplastic areas) was detected in 27% of lesions, and this was established as the cut-off point, showing the most robust association with laryngeal cancer risk ($p = 0.003$), according to this study superior to the histologic classification ($p=0.320$), the current golden standard in the clinical practice [7].

Conclusion

Although a number of identified genetic alterations shown to increase risk laryngeal precursor are emerging, none of them can be currently implemented in clinical practice as a reliable diagnostic and/or prognostic marker. Regarding the terminology of precursor lesions, dysplasia remains the most frequently used term, but squamous intraepithelial lesion can be used as a synonym as well. The term neoplasia is probably inadequate in this context. Histological findings, in spite of certain degree of subjectivity, remain at present the most reliable method for an accurate diagnosis. The current 2017 WHO classification seems to successfully stratify risk of malignant progression, with a significantly different

risk of malignant progression between LG dysplasia and HG dysplasia. In case of pronounced architectural disorders, severe cellular and nuclear atypia, and an increased number of mitoses, also atypical forms, the HG dysplasia and carcinoma in situ can be separated. Surgical removal and life-long close follow-up is a method of choice for the high-grade dysplasia/SILs. Radiotherapy is reserved for more pronounced intraepithelial lesions classified as carcinoma in situ and invasive cancer. The three-tier grading system of laryngeal dysplasia, based on the Ljubljana classification, can facilitate clinical decision of the most appropriate treatment.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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