An unusual cause of dysphonia: laryngeal verruca vulgaris

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Abstract. An unusual cause of dysphonia: laryngeal verruca vulgaris. Problems/objectives: Verruca vulgaris of the larynx (VVL) is an uncommon lesion with clinical and histopathological features that are easily misdiagnosed as verrucous carcinoma, and thus may lead to unnecessary surgery. This case study investigated clinical and pathological features that might distinguish VVL from other keratotic laryngeal lesions.

Methodology: A 35-year-old man presented with a 3-month history of progressive hoarseness and superficial, keratotic, vocal cord lesions. The verrucoid configuration of the surface and lack of nuclear atypia enabled treatment by local excision. The biopsied lesion was sectioned and examined by immunohistochemistry, and in situ hybridization.

Results: The patient was disease-free up to 1 year and 6 months after surgery. The exophytic, keratotic lesions of the larynx had features of cutaneous verruca vulgaris. No human papillomavirus was detected.

Conclusions: We described histopathological features of VVL that will facilitate its distinction from laryngeal keratosis, squamous papillomas, verrucous hyperplasia, and verrucous carcinoma.

Introduction

Verruca vulgaris is a common cutaneous lesion that is etiologically related to the human papillomavirus (HPV). It characteristically presents as one or more small, firm, elevated, nontender growths and can occur anywhere in the skin. Occasionally, it can also arise in mucous membranes, particularly in the lips, and rarely in the oral cavity and the larynx. In the latter location, it may be confused with verrucous carcinoma.

Herein, we report a rare case of benign verruca vulgaris of the larynx (VVL) that could be diagnosed by its histopathological features. The HPV type was not detected by immunohistochemical methods or in situ hybridization with biotinylated DNA probes. To our knowledge, only eight cases of laryngeal vulgaris have been reported previously, and this is the first example of VVL that was diagnosed by its unique macroscopic and histopathological features. These lesions easily may have been misdiagnosed as verrucous carcinoma, which would have led to unnecessary surgery.

Case report

A 35-year-old man presented with a 3-month history of progressive hoarseness. He had a 20-pack/year smoking history but did not consume alcohol. There were no other verrucous lesions detected in a physical examination. He also indicated that neither his wife nor children had had a history of warts.

The larynx was visualized by indirect laryngoscopy. An exophytic mass was noted on the anterior half of the left true vocal cord. The verrucous lesion did not show invasion into the subglottic area, but it did extend into the anterior comissura. The cord was not fixed (Figure 1).

We performed an excisional biopsy under direct laryngoscopy. The lesion was a firm, greyish mass that was 14 × 8 × 7 mm in size. (Figure 2). The patient’s voice improved substantially after surgery. There was no recurrence and the patient was doing well 1 year and 6 months after surgery.

Light Microscopy

The specimen was fixed in 4% neutral buffered formaldehyde solution, embedded in paraffin, sliced in 5 μm thick sections, and stained with hematoxylin-eosin for routine histological evaluation. The specimen consisted of superficial, exophytic, squamous epithelium that exhibited marked parakeratosis and papillomatosis. The lesion had a papillary, wart-like configuration due to an irregular acanthosis and papillomatosis (Figure 3). The prominent cells had large nuclei and contained numerous keratohyaline granules (Figure 4). The lesion surface consisted of occasional columns of parakeratotic cells.
Some epithelial cells with clear to vacuolated cytoplasm (koilocytes) were present diffusely throughout the upper portion of the epithelium, but were particularly concentrated between the papillary ridges (Figure 5). These cells were smaller, more hyperchromatic, and had angulated nuclei. The prominent areas of granular cells tended to be located in the troughs between two papillary ridges. A mild to moderate chronic inflammatory infiltrate was focally present at the epithelial-stromal interface. Dysplastic epithelium was not observed and there were no atypical cell forms. Mitoses were confined primarily to the basal epithelium. The malignant stromal invasion was not apparent in the basal cell layer (Figure 3). Immunoperoxidase staining and in situ DNA hybridization for HPV virus antigen failed to show unequivocally positive cells.

**Discussion**

The papilloma viruses are small DNA viruses that belong to the family of Papovaviridae. The papilloma viruses share a group-specific antigen(s), and they can be classified according to their hosts (human, bovine, etc) and the degree of nucleic acid homology. Viruses are regarded distinct genotypes when they exhibit less than 50% cross DNA hybridization.
Verruca vulgaris of the larynx

Figure 5
Some epithelial cells with clear to vacuolated cytoplasm (koilocytes) were evident.

upon reassociation in the liquid phase. As of 1990, more than 50 different genotypes of HPV have been described. 3

The papillomavirus are ubiquitous and affect both humans and animals. 3 The viruses are species-specific. There is no evidence of animal to human transmission. Human papillomavirus (HPV) is associated with a variety of lesions of the skin and mucous membranes, including verruca vulgaris, verruca planus, verruca plantaris, and condyloma acuminate. The viruses are epitheliotrophic and primarily affect the skin and mucous membranes of the genitourinary and upper aerodigestive tracts. Although differences in the histological patterns of these lesions may be due, in part, to variations in the anatomic location and host response, recent studies have shown that each HPV genotype is associated with a relatively specific clinical condition that ranges from the innocuous verruca vulgaris to life-threatening uterine cervical carcinomas. 4 Laryngeal papilloma was also linked to exposure to toxic elements, including aluminum and lead. A discussion of the various lesions is beyond the scope of this article. 4

Verruca vulgaris of the skin is one of the most common clinical manifestations of papillomavirus infections in humans. In contrast, laryngeal VV is one of the rarest manifestations of this pathology. A literature search for VVL revealed that only two publications have been reported previously. 6,7 In the first report, two of the seven patients had been misdiagnosed with verrucous carcinoma and squamous papilloma. In the first of these patients, the lesion appeared verrucous, sharply circumscribed, and elevated; also, it involved most of the left true vocal cord. In the second patient, the lesion was described as a white, exophytic lesion confined to the anterior portion of the right true vocal cord. The first patient was treated with hemilaryngectomy and the second was treated with a local excision. 6 The second publication described a case with two discrete, white, friable growths that involved the anterior portions of both right and left true vocal cords, but spared the anterior commissure. In this case, the biopsy specimen was interpreted as a verruca vulgaris, and the patient was treated with a type 1 cordectomy. Two out of the eight previously reported cases showed positive staining for papillomavirus with the immunoperoxidase technique. In the second publication, in situ hybridization with biotinylated DNA probes clearly demonstrated HPV types 6/11. 7 In contrast, our case failed to show unequivocal evidence of HPV virus antigen with immunoperoxidase staining and in situ DNA hybridization. At any given time, approximately 50% of cutaneous VV will exhibit positive staining with the immunoperoxidase technique and in situ DNA hybridization. 2,8 However, the combination of histological features was sufficient to identify these lesions as VV.

Verruca vulgaris of the skin is etiologically associated with HPV types 2 and 4; however, VV of the mucous membranes of the lips and oral cavity is related to HPV type 2 and only rarely to HPV type 4. 9,10 In one case, a biopsy specimen was demonstrated to harbor HPV types 6/11. 7 Human papillomavirus types 6 and 11 also have the same genotypes as those affiliated with multiple, sometimes solitary, papillomas of the larynx. 11

Laryngeal verruca vulgaris should be differentiated from “ordinary” keratosis, squamous papillomas, and verrucous carcinoma. All of these lesions have overlapping features, and only some of the differences are quantitative. Nevertheless, we believe that histological differentiation of these entities is possible. The “ordinary” papillary keratosis should not be difficult to diagnose. Both VVL and papillary keratosis
occur in adults and involve the true vocal cords. The granular layer is usually thin and composed of cells with very delicate keratohyaline granules, although there may occasionally be large and coarse granules. However, in contrast to VVL, papillary keratosis lacks koilocytosis. Furthermore, papillary keratosis frequently exhibits various degrees of atypia/dysplasia, which is not present in VVL.

Although multiple papillomatosis and VVL are caused by the same types of viruses, laryngeal squamous papillomas of both the multiple juvenile type and solitary adult type may also be histologically distinguished from VVL. Multiple juvenile papillomatosis, as the name implies, is a disease characterized by multiple, small, sometimes confluent, papillomas that occur primarily in children and only occasionally in adults. The papillomas appear pink upon laryngoscopic examination and typically involve the true and false vocal cords and ventricles but may also occur in other laryngeal sites, the tracheobronchial tree, oropharynx, and oral cavity. The clinical course is often protracted and is characterized by multiple local recurrences. In contrast, VVL occurs in an older age group (average age, 56 years), appears whitish on laryngoscopic examination (as in our case; Figure 1), has only been found in the true vocal cords, and recurs infrequently (17%). Both lesions exhibit koilocytosis, though it tends to be more prominent in VVL. Papillomas associated with multiple juvenile papillomatosis show little or no surface keratinization and keratohyaline granules are absent; on the other hand, VVL is heavily keratinized and contains prominent keratohyaline granules (as in our case).

It is most difficult to make a distinction between VVL and the verrucous carcinoma group of lesions. Like VVL, verrucous carcinoma of the larynx occurs in adults (median age, 58 years), exhibits a male predominance, arises primarily from the true vocal cords, and is heavily keratinized. The typical verrucous carcinoma has a dense keratotic layer, but lacks the prominent granular cell layer and the large keratohyaline granules of VVL. Keratohyaline granules are sparse to absent in verrucous carcinoma, and while koilocytic cells may be present in verrucous carcinoma, they are decidedly less common than in VVL. All descriptions of verrucous carcinoma emphasize the bullous expansion of the advancing margin of epithelium. In contrast, the rete ridges of VVL tend to be narrow and there is often considerable lamina propria between them. The rete ridges of verrucous carcinoma are usually closely packed and the rete pegs are therefore narrow and often do not reach high into the proliferating epithelial layer. The stroma of verrucous carcinoma also tends to be more heavily inflamed than in VVL. Lastly, VVL can be distinguished from verrucous carcinoma on the basis of the depth of invasion. As long as the VVL remains on a plane above the surrounding normal epithelium, it is considered VVL (Figure 3); in contrast, in verrucous carcinoma the malign stromal invasion is noted at the epithelial-stromal interface.

The incidence of laryngeal VVL has not been reported, and it is unknown to what extent it has previously been misdiagnosed as verrucous hyperplasia or carcinoma. The natural history of laryngeal VVL is also unknown. Nevertheless, VVL should be distinguished from keratosis, squamous papillomas, and verrucous carcinoma. It is particularly important to distinguish VVL from verrucous carcinoma, due to the distinct therapeutic implications. Verrucous carcinoma may require radical therapy of hemilaryngectomy, though recently, laser therapies have been found to offer better results with conservative surgery. On the other hand, VVL should be always treated with a local excision.

References

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Verruca vulgaris of the larynx

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