EDITORIAL

We have a "ring around the collar" problem

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy in the world and is associated with significant morbidity and mortality. Oral cavity squamous cell carcinoma (OCSCC) represents about a third of the 50,000 cases of HNSCC in the United States, and almost half of the 600,000 worldwide cases.[1,2] Despite the numerous therapeutic advances, the long-term survival of patients with human papillomavirus (HPV)−negative SCC remains modest. Because OCSCC is often preceded by premalignant lesions, patients with this disease benefit the most from screening and early detection. Because premalignant oral lesions cannot be accurately identified solely on the basis of their clinical characteristics, the gold standard is biopsy and histologic evaluation. However, from a diagnostic and clinical management perspective, the definition of oral premalignancy is problematic. Classic oral epithelial dysplasia (OED) is currently considered premalignant and at risk for progressing to SCC. However, the majority of these lesions will not progress to cancer, even over prolonged periods. Several studies have underscored this concept. Mincer et al. evaluated patients with OED and followed them for up to 8 years. Only 11% of the lesions underwent malignant transformation during the observation period.[3] Likewise, Arduino et al. demonstrated that the 1-year outcomes of patients with OED were highly variable, with 40% of the lesions disappearing, 20% remaining stable, 7% progressing to OCSCC, and 33% of the patients developing new lesions.[4] Finally, in a meta-analysis, the overall malignant transformation rate in nearly 1000 patients with OED was 12%.[5] Given this relatively low rate of transformation and the limited chemopreventive options, intervention has largely been conservative in nature and limited to risk reduction with careful follow-up.

However, a potentially more ominous premalignant oral condition has entered the fray. First described by Hansen, proliferative verrucous leukoplakia (PVL) appears to be a unique type of oral premalignancy.[6] Although data regarding the natural history of this disease are limited, there is a growing impression that the incidence of PVL may be on the rise. This is disconcerting on several levels because there are considerable unknowns with respect to the biology, clinical presentation, histopathologic diagnosis, treatment, and prognosis of this condition. In short, we have a great deal of work before us.

From a biologic/etiologic perspective, we have much to discern regarding the contributing factors and the molecular mechanisms driving transformation and progression. The limited data, to date, suggest that the 2 conditions may utilize different pathways of progression compared with classic OED and OCSCC.[7,8] Clinically, PVL presents as multifocal, nonhomogeneous, relentlessly growing/expanding leukoplakia. Importantly, compared with classic OED, PVL has a significantly higher rate of recurrence and malignant transformation (as high as 75%) as well as the development of second primary tumors. One can readily appreciate that this condition represents a unique and worrisome form of oral premalignancy.[6,9−12] Although PVL often affects the gingiva and buccal mucosa initially, it typically spreads to

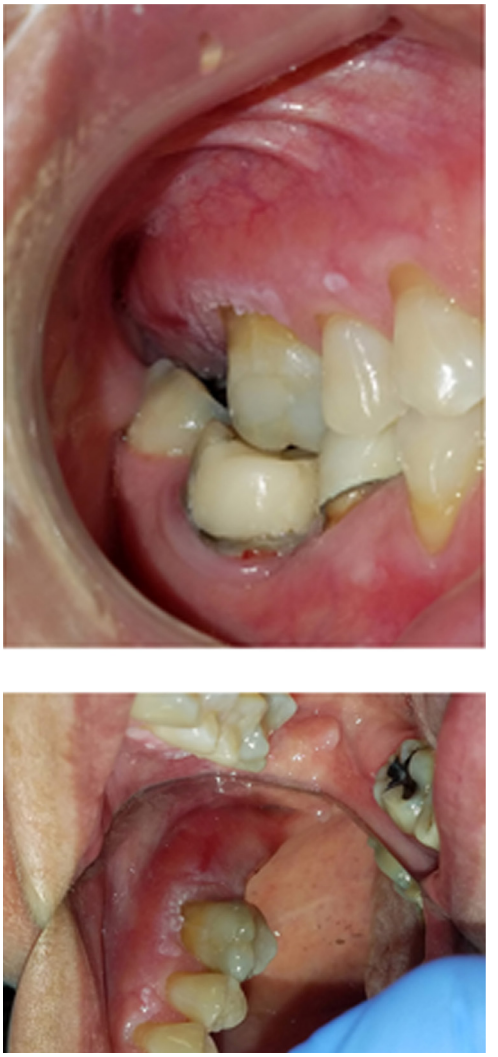

Fig. 1. Representative clinical presentation of "ring around the collar" demonstrating the multifocal appearance of proliferative verrucous leukoplakia (PVL) involving the maxillary gingiva.

other locations of the oral cavity. The gingival lesions have been described by Dr. Donald Cohen and his University of Florida colleagues as "ring around the collar" (Figure 1). I happen to like this colloquial clinical phrase when discussing this condition with general practitioners because it provides a striking visual clinical representation that seems to be limited to PVL. From a more scientifically objective perspective, in spite of numerous attempts, criteria for the clinical terminology and presentation of this condition are still in development.[6,13–15] Currently, there is lack consensus within the field of pathology with respect to the diagnostic criteria and the most appropriate diagnostic term for this condition. For example, the interesting pilot study by Upadhyaya et al. nicely demonstrated the challenges of diagnosing PVL and the subsequent downstream implications to patient management, underscoring the need for standardized diagnostic terminology and criteria.[16] Finally, from a treatment perspective, numerous different treatment modalities, including topical treatment, radiation, laser ablation, simple excision, and block resection, have been attempted.[6,10,17–23] However, we currently do not have an evidence-based standard of care.

In summary, PVL is a unique and aggressive form of oral premalignancy, which, more often than not, progresses to cancer. As discussed above, many aspects of this relatively new condition continue to remain largely unknown to us. Importantly, it represents a clinical conundrum that will require a true multispecialty collaborative effort by general practitioners, pathologists, oncologists, and surgeons to establish consistent clinical/histologic diagnostic criteria as well as evidence-based treatment guidelines. I hope that this editorial will serve to gratefully acknowledge the outstanding individuals currently investigating PVL and as an invitation to inquisitive investigators from all specialties to join the fray as we seek to combat this perplexing condition.

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