The Study of Association between Laryngopharyngeal Reflux and Vocal Fold Leukoplakia Requires Pepsin and Bile Salt Tissue Analyses

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Dear Editor,

We read the article entitled “Association between Laryngopharyngeal Reflux and Vocal Fold Leukoplakia” [1]. The authors performed hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMII-pH) in patients with vocal fold leukoplakia (VFL) to evaluate the prevalence of laryngopharyngeal reflux (LPR). They compared the results with a control group of individuals exhibiting RSI <13 and RFS <7. The authors observed a significant correlation among VFL, pharyngeal reflux events, and tobacco and alcohol consumption, with heavy drinking and acid pharyngeal events being independent factors of the occurrence of VFL. They also observed that weakly acid LPR was associated with a more severe disease [1]. They concluded that their results provide evidence for the detection of acid, weakly acid, and alkaline LPR in patients with VFL. We acknowledge the authors for this interesting study and the use of the HEMII-pH study to confirm the LPR diagnosis. We agree with the need to use HEMII-pH testing to detect LPR but, prior to recommending the systematic detection of LPR in patients with VFL, we need to confirm the relationship between reflux and VFL. Indeed, the observations of the authors did not confirm the causal

relationship. In this study, nearly half of the patients smoked ≥ 20 cigarettes per day, while the remaining patients were categorized as “nonheavy smokers” consisting of patients who smoked <20 cigarettes daily. In fact, we have no details about the proportion of nonsmokers or individuals without tobacco history. Similar observations are made for drinkers. This point is particularly important.

First, to date, tobacco is still the most important favoring factor of VFL [2]. Because the majority of patients smoked, it is conceivable that tobacco remained the main causal factor of the development of their VFL. Second, it has been demonstrated that tobacco (nicotine) and alcohol decrease the esophageal sphincter pressure, leading to transient relaxations and related reflux events [3, 4]. In that way, VFL and LPR may be both related to tobacco consumption and may be not necessarily linked. The authors mentioned in the discussion the potential role of pepsin in the destruction of the laryngopharyngeal mucosa. Pepsin is known to alter the mucosal defense mechanisms, that is, mucin production, anhydrase carbonic activity, and growth factor secretion, leading to the occurrence of epithelial microtrauma, dehiscence, and lesion [5]. The detection of pepsin and other gastroduodenal en-

zymes in VFL is the missing element to really support more than a simple association between pharyngeal reflux events and the development of VFL. The study by Lu et al. [6] is an important clinical step in the understanding of the potential role of LPR in the development of VFL. We encourage the authors to perform gastroduodenal enzyme (e.g., pepsin, bile salts, and trypsin) immunohistochemical analyses in the leukoplakia tissues to better understand the role of acid, weakly acid, and alkaline LPR in the development of VFL. The consideration of other gastroduodenal enzymes and not only pepsin particularly makes sense regarding the potential role of bile acids, weakly acid and alkaline LPR, in the development of laryngeal and pharyngeal cancers [6, 7]. The consideration of patients with VFL without tobacco or toxic history is another important point to distinguish the role of tobacco versus the role of reflux in the development of these usual VF lesions.

References

- 1 Lu G, Ding X, Xu W. Association between laryngopharyngeal reflux and vocal fold leukoplakia. *ORL J Otorhinolaryngol Relat Spec*. 2021;83:159–66.
- 2 Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. *Lancet*. 2008; 371(9625):1695–709.
- 3 Ness-Jensen E, Lagergren J. Tobacco smoking, alcohol consumption and gastro-oesophageal reflux disease. *Best Pract Res Clin Gastroenterol*. 2017;31(5):501–8.
- 4 Bhandarkar PV, Shah SK, Meshram M, Abraham P, Narayanan TS, Bhatia SJ. Effect of acute and long-term oral tobacco use on oesophageal motility. *J Gastroenterol Hepatol*. 2000;15(9):1018–21.
- 5 Klimara MJ, Randall DR, Allen J, Figueredo E, Johnston N. Proximal reflux: biochemical mediators, markers, therapeutic targets, and clinical correlations. *Ann N Y Acad Sci*. 2020; 1481(1):127–38.
- 6 Tutar H, Erdamar H, Köybaşıoğlu A, Dinç AE, Ceylan A, Uslu S. Can bile acids be an etiological factor for laryngeal carcinoma? *ORL J Otorhinolaryngol Relat Spec*. 2011; 73(3):156–61.
- 7 Shellman Z, Aldhahrani A, Verdon B, Mather M, Paleri V, Wilson J, et al. Bile acids: a potential role in the pathogenesis of pharyngeal malignancy. *Clin Otolaryngol*. 2017;42(5): 969–73.

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