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LETTER TO THE EDITOR

Assessing actinic cheilitis oncogenic potential via micronucleus assay

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Dear Editor,

Actinic Cheilitis (AC) is a chronic inflammatory condition caused by prolonged solar radiation, characterized by a spectrum of clinical-morphological alterations including dryness, ulceration, fissures, and atrophy (Vasilovici et al. 2022). In general, the disease progresses slowly and asymptomatically, with most cases being associated with the development of *in situ* squamous cell carcinoma (SCC) of the lip (Vasilovici et al. 2022). Similar to other alterations in the oral cavity, AC is diagnosed through oral biopsy surgery, a procedure that may compromise tissue stabilization failures (Shah et al. 2023, Jeng et al. 2024). Given the clinical relevance of AC and the need for monitoring to prevent its progression to oral cancer, we discuss in this letter the potential integration of the micronucleus assay (MN assay) as an auxiliary diagnostic tool and its incorporation into oral medicine services.

A micronucleus (MN) is an extra-nuclear anomalous body containing chromosomal fragments that originate from mis-segregation during mitosis (Di Bona & Bakhoum 2024). In cancer cells, this structure is chromosomally unstable and has been associated with tumor progression as well as genomic, epigenetic, and transcriptional alterations that increase the risk of mutagenicity (de Souza et al. 2022). The MN assay is typically performed on samples collected via exfoliative cytology, and its analysis can reveal cellular morphological features while also aiding in the early diagnosis of oral premalignant lesions (Elnaggar et al. 2023, Caponio et al. 2024). Given that AC is characterized by genomic instability in keratinocytes exposed to solar radiation (Shah et al. 2023), it can be investigated by exfoliative cytology, which may help assess the risk of malignant transformation in the oral mucosa.

Traditionally, exfoliative cytology is considered a non-invasive, painless, low-cost, and easy-to-perform technique (Caponio et al. 2024). As a result, this approach may aid in monitoring AC progression and assessing its clinical response of the disease to current therapeutic modalities (e.g., Photodynamic therapy and Topical agents). Due to its benefits and wide applicability in micronucleus analysis, several authors have discussed its use for monitoring oral potentially malignant disorders

(OPMDs) (de Souza et al. 2022). For instance, Elnaggar et al. (2023) demonstrated that the accuracy of the MN assay was higher in individuals with OPMDs (i.e., leukoplakia) compared to the control group. Similarly, Bhatnagar et al. (2023), who investigated exfoliated cell samples from the buccal mucosa of patients with SCC, oral submucous fibrosis, and leukoplakia, concluded that MN may be an effective biomarker for monitoring OPMDs, particularly in misdiagnosed cases.

However, the MN assay requires the use of DNA-specific stains such as Feulgen, 4', 6-diamidino-2-phenylindole dihydrochloride (DAPI), and Acridine orange to prevent the risk of diagnostic confusion as well as under- or overestimation of MN count (Naderi 2020). In turn, this protocol contrasts with the usual stains used in pathology services (e.g., Papanicolaou stain, Hematoxylin and Eosin), which are considered less precise for MN detection. This discrepancy implies additional costs-for acquiring specific reagents (Naderi 2020, Ayres et al. 2023). Nevertheless, preliminary findings support the use of the MN assay as a diagnostic adjunct to biopsy for identifying OPMDs (Bhatnagar et al. 2023, Elnaggar et al. 2023). Although still unexplored, cutaneous lesions caused by high levels of solar radiation, exacerbated by climate changes, have been identified as a potential contributor to the rising incidence of skin cancer (Watson et al. 2024). Intriguingly, this aspect draws attention to the potential emergence of new AC cases, highlighting to incorporate alternative diagnostic methods for the rapid detection of this condition.

Therefore, the MN detection test is an invaluable tool for detecting abnormal cellular changes before cancer develops. Additionally, more extensive epidemiological studies and larger population samples are necessary to validate the application of this technique to other conditions relevant to Oral Medicine.

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