

Case Report

Negative autofluorescence in benign exophytic lesions highly suspicious for malignancy: importance of the tool as a rapid screening method for lesions requiring biopsy

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ARTICLE INFO

Keywords:

Autofluorescence
460 nm diode lamp
Negative autofluorescence
Oral malignant lesions
Oral exophytic lesions

ABSTRACT

Autofluorescence (AF) is a system based on the physiological presence of endogenous fluorochromes in the oral mucosa that change concentration in neoplastic tissues.

When exposed to 450–470 nm-blue light, normal tissues emit a light green fluorescence, whereas pre-neoplastic and neoplastic tissues show a loss of AF, so they appear as dark green/black areas when viewed through appropriate wavelength-filtering eyewear. Benign reactive lesions of the oral cavity can sometimes enter the differential diagnosis with malignant tumors. We present two clinical cases of irregular exophytic highly suspicious lesions in which the use of autofluorescence played a decisive role in the differential diagnosis.

1. Introduction

Autofluorescence (AF) is a phenomenon, well described in the medical field, based on the physiological presence of endogenous fluorochromes such as nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FAD) in the tissues of the oral mucosa [1]. These molecules, emit fluorescence in the green spectral range when excited by light with a wavelength of 370–460 nm. Fluorochromes concentration changes in neoplastic tissues; for example, due to disruption of cross-linked collagen and we can observe a reduction of the ratio of FAD to NADH compared to normal cells [2]. These phenomena explain why normal tissues show a light green fluorescence, whereas pre-neoplastic and neoplastic tissues show a loss of autofluorescence, so they appear as dark green/black areas [3].

Among the AF devices on the market, we can find a system that uses specific glasses and the lamp that is commonly used in dental offices for composite polymerization, which emits blue light with a wavelength between 450 and 470 nm [3].

Among the benign reactive lesions of the oral cavity—characterized by epithelial cell hyperproliferation driven by chronic inflammatory or irritative stimuli—are the traumatic fibroma and the pyogenic granuloma [4]; both are exophytic lesions with a very high prevalence in the population. The fibroma generally presents as a normochromic lesion—sometimes featuring white hyperkeratotic areas—with a firm,

elastic consistency. The pyogenic granuloma is more commonly pedunculated, reddish-purple in color, soft in consistency, and highly vascularized, with a tendency to bleed and recur [5]. Although neither lesion possesses malignant transformation potential, they can sometimes exhibit highly irregular shapes and reach significant sizes, necessitating a differential diagnosis that includes squamous cell carcinoma [5].

Squamous papilloma is a benign, exophytic, pedunculated lesion—typically irregular in shape and normal in color—of an infectious nature linked to HPV infection. The presence of dysplasia within these papillomas classifies them among the potentially malignant disorders of the oral cavity [6].

Several cases of lesions initially presenting as squamous papillomas have progressed to squamous cell carcinomas [6], for this reason AF could therefore help distinguish benign reactive lesions—such as fibromas, pyogenic granulomas, and squamous papillomas—from malignant ones.

The aim of this paper is to present two clinical cases of irregular exophytic lesions in which the use of AF played a decisive role in the differential diagnosis.

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<https://doi.org/10.1016/j.pdpdt.2026.105623>

Received 15 July 2026; Received in revised form 13 August 2026; Accepted 19 August 2026

Available online 20 August 2026

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2. Case presentations

2.1. Patients and methods

Both patients were assessed and treated in the Otorhinolaryngology Department of the Cagliari University Hospital (Monsserrato).

AF examinations were performed using a simple AF system of previously proven effectiveness [3]. The system comprises Goccles® eyewear (Pierrel, Milan, Italy) and an LED light with a wavelength of 420–480 nm (peak at 460 nm) and power of 5 W (Woodpecker, Ravenna, Italy). This light source is typically used in dental offices for composite polymerization. The optical filters of the Goccles® eyewear consist of a three-layer laminar optical structure that transmits the AF emission from FAD (515 nm) while blocking other visible and ultraviolet wavelengths, including the blue excitation light from the LED lamp. AF viewing was performed wearing this filtering eyewear and with the lamp positioned approximately 1–2 cm from the oral tissues for 1 min of total illumination. The tissue irradiance was approximately 1400 mW/cm².

Case 1. A 70-year-old female patient with no significant systemic medical history presented with an erythematous, exophytic lingual lesion that had developed two weeks after the removal of a previous carcinoma in situ. The lesion, measuring 12 mm in maximum diameter, was non-tender and felt elastically tense upon palpation. The patient had observed it enlarging over the 14 days following the excision of a 10 mm erythroplakia on the right lingual margin, which had been diagnosed as squamous cell carcinoma in situ. Given the previous diagnosis, there was a high probability that the lesion was malignant.

AF was performed using The Goccles® _device previous described. AF testing was negative, showed homogeneously bright green tissue consistent with a benign lesion (Fig. 1).

A new biopsy had already been scheduled at the same department where she had undergone the first procedure, for diagnostic purposes, as is routinely done in cases like this of recurrent lesions. So the patient underwent a repeat excisional biopsy and histological evaluation, performed in the same University Hospital, which confirmed the presence of an oral reactive lesion consistent with a pyogenic granuloma. The prior resective surgery, which involved the use of silk sutures, may have been the triggering event for the benign neoplasm. Completely negative AF was consistent with the histological result.

Case 2. A 77-year-old male patient was an urgent referral requiring rapid case assessment. He had a history of previously diagnosed metastatic prostate carcinoma and presented with an exophytic lesion

on the mandibular gingiva in an edentulous area. The lesion was asymptomatic, had been present for several months, and prevented the insertion of his removable prosthesis. Clinical examination revealed a sessile lesion with a highly irregular, verrucous shape and a maximum diameter exceeding 2 cm; the appearance was consistent with either an oral metastasis from prostate carcinoma or squamous cell carcinoma.

AF examination, showed bright green tissue across the entire area, with no distinction from the surrounding tissue, and was therefore interpreted as negative (Fig. 2). The lesion was subsequently completely excised in the University Hospital and underwent histological examination, as is routinely done for diagnostic purposes, which confirmed a diagnosis of benign hyperplasia with a superimposed squamous papilloma, in the absence of cellular atypia.

Completely negative AF was consistent with the histological result.

3. Discussion

In both cases described, autofluorescence proved highly useful in ruling out malignant lesions in patients with a potential diagnosis of squamous cell carcinoma or oral metastasis. Oral metastases account for 1% of all metastases, with 25% being diagnosed prior to the primary tumor. In men, prostate carcinoma is among the primary tumors that most frequently metastasize to the oral cavity; this is why the possibility of mandibular gingival metastasis was considered in clinical case 2 [7].

Here, the negative AF findings reassured patients awaiting the histological results of an excisional biopsy; this confirms the technique's utility in oral pathology as a primary diagnostic tool for determining the urgency of a biopsy—which remains the gold standard for diagnosis and an essential part of the assessment.

The specificity and sensitivity values of autofluorescence systems reported in the scientific literature vary widely. This variability is partly attributable to the fact that assessments were frequently performed by clinicians lacking expertise in oral pathology or by students [8,9]. A recent study highlights the significant impact of autofluorescence systems on the diagnosis of negative cases [9], reporting negative predictive values of 91.18% (95% CI: 87.66%–94.69%). The authors reported that although the number of false-positive intercepted, AF test “can serve to alleviate patient anxiety regarding suspicious mucosal lesions in a general practice setting due to high negative predictive value”. Furthermore, a false-positive result implies overestimating the severity of the lesion—an error that is less serious than a false-negative result, where the lesion's severity goes unrecognized and it is mistakenly



Fig. 1. On the left, the clinical appearance upon inspection of a sessile exophytic lesion that developed following the removal of lingual carcinoma in situ. On the right, AF examination shows no loss of AF signal, interpreted as a negative result. This finding is consistent with the subsequent histological examination.

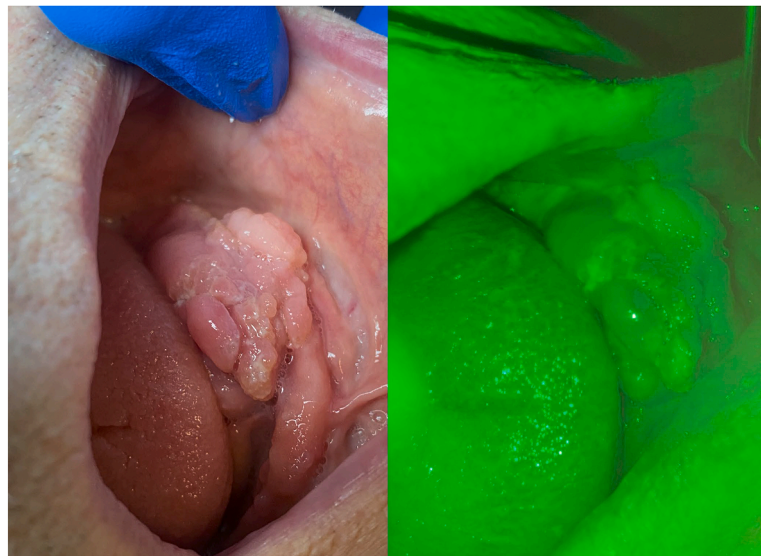


Fig. 2. On the left, a highly irregular, sessile, exophytic lesion on the mandibular gingiva of a male patient with a previous diagnosis of metastatic prostate cancer. On the right, AF examination reveals no loss of fluorescence, interpreted as a negative result. This finding is consistent with the subsequent histological examination.

deemed benign. This is why the ability to predict a negative result using the AF test—even when the lesion is clinically highly suspicious—indicates the reliability of the assessment; in any case, such evaluations must be performed by clinicians expert in oral pathology.

Although biopsy and histological examination remains the mandatory gold standard for assessment and diagnosis, our clinical experiences confirm the value of AF in a hospital setting where the number of observed lesions requiring biopsy is very high and AF has considerable value in determining the urgency of scheduling biopsies for patients with suspicious oral lesions.

Informed consent statement

Patients signed a written informed consent form for the clinical examination and diagnostic autofluorescence imaging, as well as for the anonymous acquisition of photographs. The principles of the Declaration of Helsinki were adhered to.

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This work has not received funds.

CRedit authorship contribution statement

Cinzia Casu: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Germano Orrù:** Writing – review & editing, Validation, Supervision.

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