

## Up-to-Date Review And Case Report

# Localized gingival erythroleukoplakia in a 57-year-old Fanconi anemia patient: a case report

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**Abstract** – Fanconi anemia is an extremely rare genetic disorder that has several modes of presentations, and it can lead to multiple hematological malignancies and malignant solid tumors, especially squamous cell carcinoma. Erythroleukoplakia is a rare oral mucosal disorder, associated with a high risk of malignant transformation. We report a rare case of localized gingival erythroleukoplakia in a 57-year-old female patient with Fanconi anemia that eventually revealed to be gingival *in situ* squamous cell carcinoma. Early surgical excision was performed but two local recurrences occurred. Early treatment of the recurrences allowed for adequate management of the oral malignancy. The present case aims to underline the need for thorough clinical examination and regular follow-up sessions in the early detection of premalignant and malignant conditions, especially in patients with diseases predisposing to oral cancer.

## Introduction

Fanconi anemia (FA) is an extremely rare inherited condition that has a varied presentation. It affects approximately 1 in 350 000 people, and increases the risk of multiple hematological malignancies and malignant solid tumors, such as squamous cell carcinoma (SCC) [1].

Erythroleukoplakia is a rare oral mucosal disorder associated with a high risk of malignant transformation. Management of such lesions requires regular clinical and histological follow-up examinations to detect early-stage SCC [2].

We present the case of a 57-year-old female FA patient who presented with localized gingival erythroleukoplakia, which eventually revealed to be gingival *in situ* SCC. Diagnosis and management of gingival erythroleukoplakia in the context of SCC-predisposing FA is discussed, underlining the necessity of thorough oral mucosal clinical examination in FA patients.

## Observation

A 57-year-old female patient was admitted to the department of oral surgery on 10/17/2014 for the assessment of an asymptomatic red gingival lesion that did not regress

despite adequate periodontal therapy. She suffered from an atypical mild form of FA, an extremely rare genetic disease, diagnosed 10 years before. This diagnosis, initially established on the basis of clinical criteria in 1996, had been definitively confirmed in 2004, after positive chromosome breakage tests, Western blot assay (evaluating the pathological absence of FANC-D2 protein ubiquitination, often seen in FA patients), and fibroblast DNA gene sequencing revealing two heterozygotic mutations in the FANCA gene.

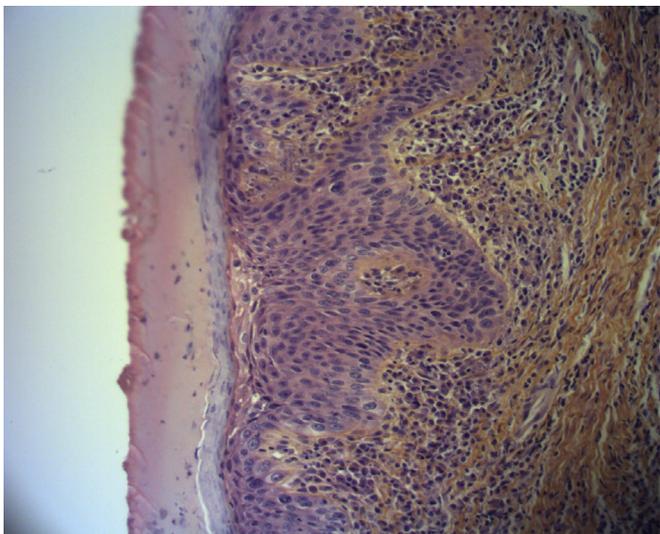
Her recent medical history also showed osteoporosis, osteoarthritis, early menopause, gastric reflux, diarrhea, kidney cysts, and severe thrombocytopenia. She also reported a past history of smoking between the ages of 19 and 29 (10 PA). She declared taking darbepoetin alfa 500 µg (1 injection monthly), escitalopram 5 mg (1 tablet daily), and vitamin D (1 vial monthly; 200,000 IU).

Clinical extraoral examination revealed a short stature, several hypochromic lenticular macules on her arms and legs, no regional lymphadenopathy, or any other significant symptoms. Intraoral examination revealed an asymptomatic localized erythroleukoplakia on the buccal gingiva of teeth 44–47 (Fig. 1). Pulp testing, percussion tests, and periodontal probing of these four teeth were strictly normal, and panoramic radiography revealed neither dental or periapical pathologies nor periodontal bone loss. Systematic examination of the oral mucosa revealed no other significant findings.

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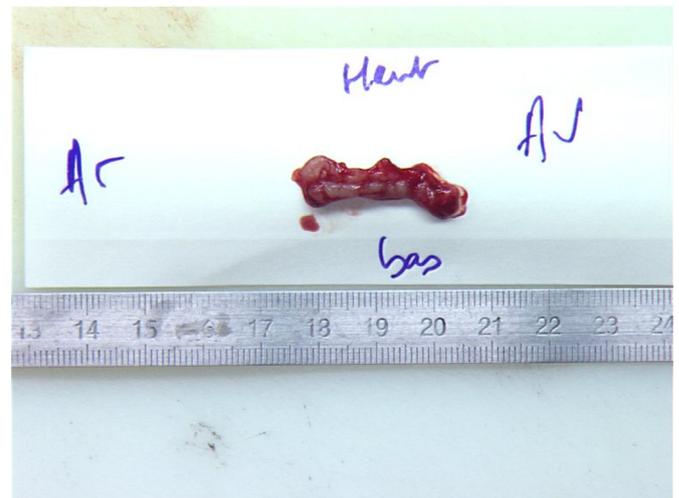
**Fig. 1.** Localized erythroleukoplakia on the buccal gingiva of teeth 44–47.



**Fig. 2.** Hematoxylin and eosin-stained histological section of gingival erythroleukoplakia revealing severe epithelial dysplasia.

Differential diagnosis of localized gingival erythroleukoplakia included gingival erosive lichen planus, necrotizing gingivitis, and gingival SCC. This patient had several oncological risk factors, including FA, past history of smoking, and previous upper aerodigestive tract malignancy. Severe gingival dysplasia or gingival SCC were potential diagnoses as erythroleukoplakia is often histopathologically associated with severe epithelial dysplasia, if not malignancy [2], and because of the patient's positive medical history.

A gingival incisional biopsy was performed in an in-patient hospital setting, at the Head and Neck Oncology Unit of the *Institut Curie*, as severe thrombopenia required specialized management. Hematoxylin and eosin-stained sections revealed histological aspects of severe dysplasia, namely: irregular rete ridges, multiple cytoarchitectural anomalies, significant parakeratosis, and high mitotic activity (Fig. 2). Considering the high risk of oral malignancy of this patient, complete surgical excision was chosen. Surgical excision of gingival erythroleukoplakia was performed under local anesthesia by gingivectomy of the affected



**Fig. 3.** Surgical specimen after gingivectomy of the affected gingiva.

buccal gingiva from teeth 43–47 (Fig. 3), which was followed by immediate coverage of excision site with a local advancement cheek flap. Postoperative recovery was uneventful apart from a spontaneously resolving zygomatic hematoma, with normal oral food intake being reestablished within 4 days.

Histopathological analysis of the surgical specimen revealed multiple fibroinflammatory changes, hyperplasia with architectural disorganization, atypical cells throughout the whole epithelium and the absence of microinfiltrations of the basal membrane. Eventually, a 25-mm-wide ulcerated *in situ* SCC was diagnosed.

When the patient returned to our department, 1 month after surgery, normal partial healing of the surgical site was observed (Fig. 4).

Regular follow-up examinations were scheduled between the *Institut Curie* and our department. Three months after the procedure, surgeons from the *Institut Curie* noted a new area of erythroleukoplakia on the lingual gingiva between teeth 44 and 45, which persisted at the next follow-up performed in our department 2 months later (Fig. 5). In agreement with the surgeons from the *Institut Curie* center, a regular follow-up of the lesion was advised.

In December 2015, 10 months after the oncological surgery, a routine follow-up examination revealed no change in aspect of the lingual gingival erythroleukoplakia between teeth 44 and 45, but also revealed a new erythematous lesion on the buccal gingiva of tooth 46 with spontaneous bleeding, highly suggestive of a local recurrence of her *in situ* gingival SCC. The patient was sent back to the *Institut Curie* center for surgical excision of the suspected recurrence of gingival SCC, but histopathological analysis of the new surgical specimen revealed mild dysplasia. Further follow-up examinations have not revealed any new recurrences to date.

## Discussion

FA is an extremely rare autosomal recessive genetic disorder with a prevalence of 1 in 350 000 births [3], first described in 1927 by Guido Fanconi [4], involving mutations



**Fig. 4.** Clinical aspect of gingiva at 1 month after surgery.



**Fig. 5.** New erythroleukoplakia on the lingual gingiva of teeth 44–45 observed at the 3-month follow-up.

in 1 of 15 genes implicated in DNA repair. It is a genetically determined DNA-instability disease characterized by various congenital abnormalities (such as short stature, microcephaly, abnormal thumbs, skin pigmentations, and/or renal malformations), progressive bone marrow failure, and predisposition to cancer [3].

Because of the severe hematological disorders, patients with FA are often subjected to hematopoietic stem cell transplantation (HSCT), which is associated with a 4.4-fold increased risk of SCC development compared to nontransplanted FA patients [5].

The high predisposition for cancer in FA patients stems from mutations of caretaker genes, *i.e.*, genes implicated in DNA repair mechanisms. As such, inactivation of caretaker genes is considered to promote indirect carcinogenesis by facilitating genetic instability, in turn leading to increased mutations of all genes, including gatekeeper genes (genes that control cell growth or promote cell death) that will eventually lead to cancer development [6]. More specifically, patients will initially acquire a single mutant allele of a caretaker gene from an affected parent and will only develop cancer after three further somatic mutations, *i.e.*, the remaining allele and both alleles of the gatekeeper gene [6]. In a study of all published cases of FA between 1927 and 2001, there were 220 cases of cancer development out of 1301 total cases of FA, with a mean age at diagnosis of 14.5 years for leukemias, 22.6 years for solid tumors (of which 48% were Head and Neck carcinomas), and 15.7 years for liver tumors [7]. These findings suggest that these cancer-inducing mutations occur quite rapidly in the disease course. Furthermore, HSCT-related complications such as immunosuppression, myelosuppression, graft-versus-host-disease, and/or infections could promote head and neck solid tumor development in such patients (with a crude estimated risk of 42% at 12 years after transplant), mostly primary tongue carcinomas [7].

As FA is an extremely rare disease, little attention has been given to oral manifestations of the disease. Oral manifestations include missing or supernumerary teeth, microdontia, root shape anomalies, tooth malpositioning, susceptibility to

dental caries, gingival and periodontal diseases, oral mucosal lesions (ulcerations), salivary gland dysfunction (of endocrine origin), and a significant propensity to develop oral cancer, such as SCC [3]. As the bone marrow failure worsens during the course of the disease, the patients will develop mucosal pallor, neutropenic ulcers, local infections, petechiae, hematomas, and spontaneous gingival bleeding. Regarding precancerous conditions, a cross-sectional study including 138 patients with a median age of 9 years revealed that 12% patients exhibited at least one leukoplakia lesion [8]. A recent systematic review reported a malignant transformation rate of leukoplakia varying between 0.13% and 34% cases [9], which is probably much higher in FA patients.

The present case is interesting in several respects. The patient presented with a very mild form of FA, as most patients have a mean life expectancy of 25 years [10] and this patient was 57-year-old at the time of first consultation. This can, at least partially, be explained by the heterozygous mutations involved in the pathogenesis of this patient’s FA. Furthermore, despite the mild course of her disease, the patient experienced two different episodes of malignancy (esophageal carcinoma and gingival *in situ* carcinoma), thus underlining the high propensity of cancer development in such patients [6]. As in the present case, malignancy recurrence in FA patients is often a significant issue as shown in the prospective study by Kutler *et al.*, who found that among the 19 FA patients who developed SCC, 10 (53%) developed locoregional recurrences within a median of 16 months after diagnosis [11]. In this patient, recurrence occurred 26 months after the first gingival SCC diagnosis. Finally, considering the high malignant transformation rate of erythroleukoplakia, even in non-FA patients [2], a thorough clinical examination is necessary to detect early malignant changes and help improve the patient’s prognosis. In the present case, regular follow-up and early management allowed for rapid detection of local gingival SCC recurrence. In FA patients with a history of leukoplakia or recurrent oral lesions, head and neck examinations are recommended every 6–8 weeks [12].

## Conclusion

Considering the high hematological and oncological burden in FA patients, a through systematic clinical examination and regular follow-up visits are mandatory for detecting early oral pathological changes, indicative of malignancy development. Although some authors have suggested self-examination of the mouth for oral cancer screening in high-risk FA patients [13], regular examination by an oral medicine specialist must be encouraged in these patients.

**Conflicts of interests:** The authors declare that they have no conflicts of interest in relation to this article.

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