J. Oral Diagn 2025;10:e378
https://doi.org/10.5327/2525-5711.378

CASE REPORT

Therapeutic challenges of recurrent oral squamous cell carcinomas in fanconi anemia: a case report

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Abstract

Fanconi anemia (FA) is a rare, inherited recessive syndrome characterized by progressive bone marrow failure and a predisposition to developing malignant neoplasms. A male patient diagnosed with Fanconi anemia underwent a haploidentical hematopoietic cell transplantation (HCT) at 10 years of age. Eleven years later, he developed his first malignant lesion on the lower lip. Unfortunately, the patient experienced rapid recurrences of squamous cell carcinoma (SCC), initially in the oral cavity, with subsequent progression to the maxillary sinus, sphenoid wing, and right orbital floor. The aggressive nature of the disease, coupled with limited treatment options, ultimately led to a poor prognosis and the patient subsequently passed away. This case underscores the severity of Fanconi anemia, demonstrated by the emergence of multiple lesions in diverse locations and their rapid progression in a young patient. It highlights the complexity and significant challenges in managing malignant lesions in patients with FA.

Keywords: Carcinoma; Oral cancer; Fanconi Anemia

INTRODUCTION

Fanconi anemia (FA) is a rare, inherited recessive syndrome characterized by progressive bone marrow failure and an increased predisposition to developing malignant neoplasms, including leukemia and solid tumors. Hallmark features of FA include skeletal malformations, melanotic pigmentation (café-au-lait spots), and developmental delay[1,2].

Hematopoietic cell transplantation (HCT) is the treatment of choice for restoring bone marrow function in these patients. However, the risk of developing neoplasms, particularly squamous cell carcinoma (SCC) in the head and neck region, progressively increases after HCT due to both genetic factors and treatment-related complications[1,2]. Given these predisposing factors, regular monitoring and early identification of oral lesions are critical, as there is no predictability regarding the emergence of cancerous fields[3,4]. Early diagnosis is critical in patients with Fanconi anemia due to their marked hypersensitivity to the cytotoxic effects of radiotherapy and chemotherapy, which are generally contraindicated owing to the high risk of severe, potentially life-threatening complications.

Statement of Clinical Significance
This case highlights the need for continuous oral surveillance in Fanconi anemia patients, given the early, aggressive, multifocal presentation of squamous cell carcinomas. Early diagnosis and personalized management are essential to overcome limitations of conventional screening and improve patient outcomes.

The aim of this study is to report a case of a patient with Fanconi anemia who developed oral tumors with early recurrences in uncommon and challenging topographic regions.

CASE REPORT

A 21-year-old male patient was admitted to the Referral Hospital at the age of 8 for diagnostic investigation due to skin spots and nasal bleeding. He was diagnosed with Fanconi anemia, confirmed through cytogenetic testing. At age 10, due to bone marrow aplasia, the patient underwent a haploidentical hematopoietic stem cell transplantation, with his mother as the donor. Following the treatment,

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Received on June 19, 2025. Accepted on September 2, 2025.
https://doi.org/10.5327/2525-5711.378

the patient developed graft-versus-host disease (GVHD) affecting the liver, intestines, and oral cavity, presenting with lichenoid lesions and scattered leukoplakia.

Given the high predisposition to neoplasm development associated with the syndrome, routine annual multidisciplinary follow-up consultations were established. Oral lesions suspected of malignancy were occasionally evaluated through biopsies or non-invasive methods, such as exfoliative cytology, which facilitated ongoing monitoring and enhanced the patient's adherence to follow-up care. At 21 years of age, during a routine dental check-up, an erythroleukoplastic lesion approximately 1 cm in size was observed in the median region of the lower labial mucosa. An incisional biopsy revealed mucosa with compact hyperkeratosis overlying a thickened epidermis containing rare necrotic keratinocytes. Melanophages were observed in the lamina propria. No significant inflammatory infiltrate was identified. The histological findings are suggestive of a late-stage lichenoid-pattern pathological process. From that point on, the patient began presenting with suspicious lesions in various locations as shown in Figures 1 and 2. The diagnoses and treatments administered were also detailed in the Table 1.

Unfortunately, the patient experienced numerous recurrences of squamous cell carcinoma within a short period, initially in the oral cavity, progressing to the maxillary sinus, sphenoid wing, and right orbital floor (Figure 3), associated with facial swelling on the right side and difficult-to-control pain. Ultimately, the tumor was deemed unresectable, and the patient was under the care of the oncology and palliative care teams. The disease progression and limited treatment options led to the patient's death 29 months after first tumor diagnosis.

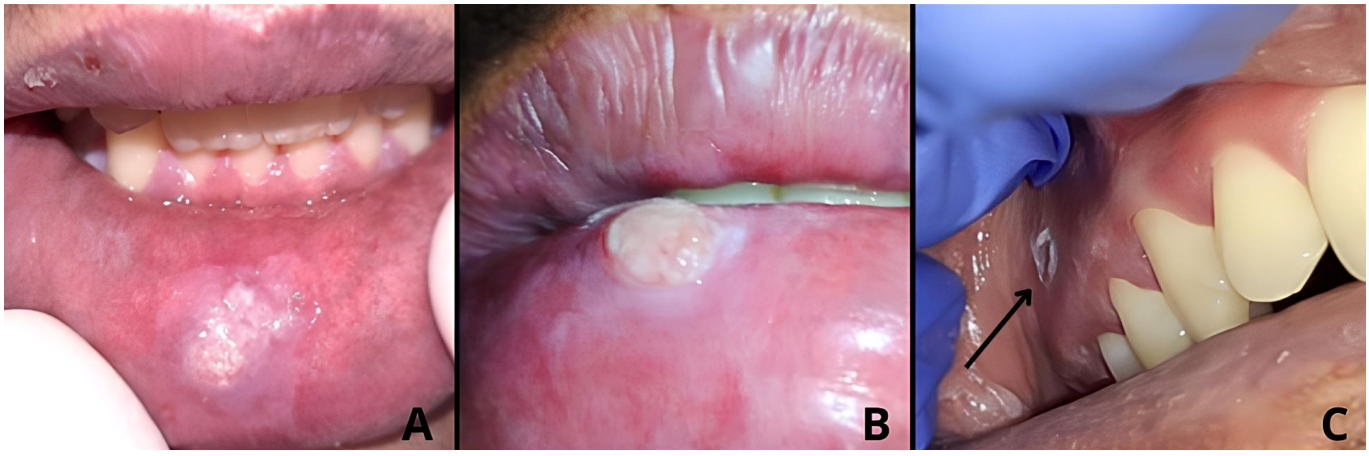

Figure 1. (**A**) Erythroleukoplastic lesion on the lower labial mucosa, with irregular edges, measuring 1 cm in its longest extent. (**B**) Exophytic erythroleukoplastic lesion with a rough surface, on the lower labial mucosa, measuring 1 cm in length. (**C**) Erythroleukoplastic lesion on the right upper jugal mucosa, with an irregular surface, measuring 1.8 cm in length.

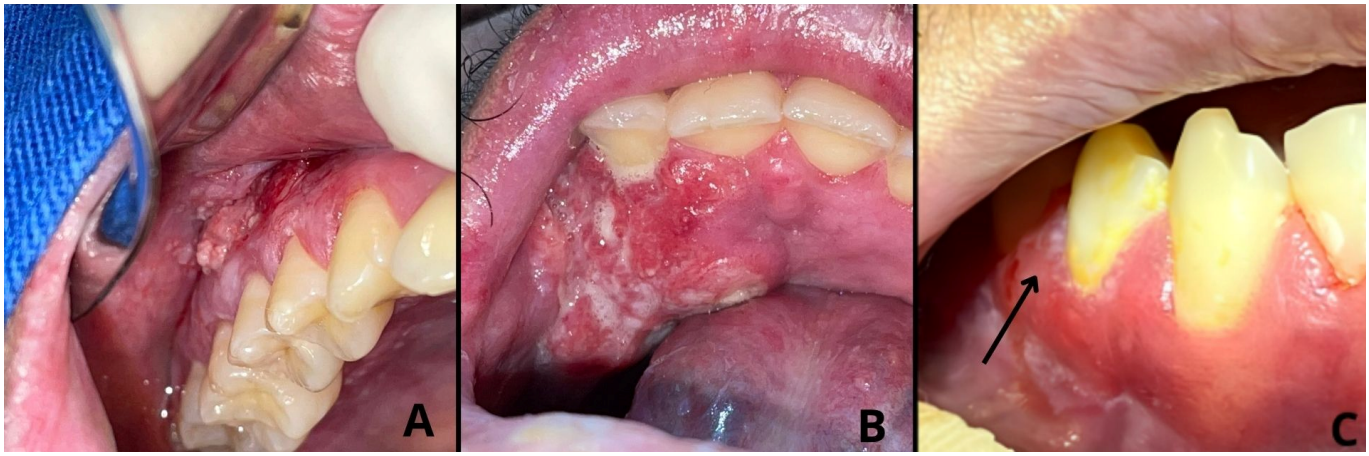

Figure 2. (**A**) Erythroleukoplastic lesion with a verrucous appearance on the upper right gingival border, measuring 1.5 cm in length. (**B**) Erythroleukoplastic lesion with a verrucous appearance, with the presence of ulcerated areas, on the upper right gingival border, lateral to the right lateral incisor, measuring 1.5 cm in length. (**C**) Erythroleukoplastic lesion on the lower right marginal and inserted gingiva, close to the lower right first premolar.

Table 1 – Timeline of lesion's diagnosis and treatments.

Timeline (months after first diagnosis)	Oral Lesion characteristics	Site	Histological Diagnosis	Treatment
First diagnosis Fig. 1A	Erythroleukoplakia, 1cm	Inferior Labial mucosa	Chronic lichenoid-pattern lesion	Follow-up
7 months Fig. 1B	Exophytic erythroleukoplakia with irregular surface, 1 cm	Inferior Labial mucosa	Well-differentiated SCC	Surgery with neck dissection
12 months Fig. 1C	Painful nodular erythroleukoplakia, with 1.8cm 1 month evolution	Buccal mucosa, right side	Mild dysplasia	Follow-up
19 months Fig. 2A	Painful verrucous lesion with foul odor and 1.5 cm	Right upper gingival ridge	Well-differentiated, superficially invasive SCC	Surgery
22 months Fig. 2B	Painful verrucous lesion with foul odor and 1.5 cm	Right upper gingival ridge, incisive area	Well-differentiated, superficially invasive SCC, with perineural invasion	Hemimaxillectomy
26 months	Right maxillary volume augmentation, painful	Maxillary subcutaneous tissue.	Moderately differentiated SCC	Surgery and clinical oncology evaluation
27 months Fig. 2C	Friable erythroleukoplakia	Right marginal and inserted gingiva	SCC	Paliative

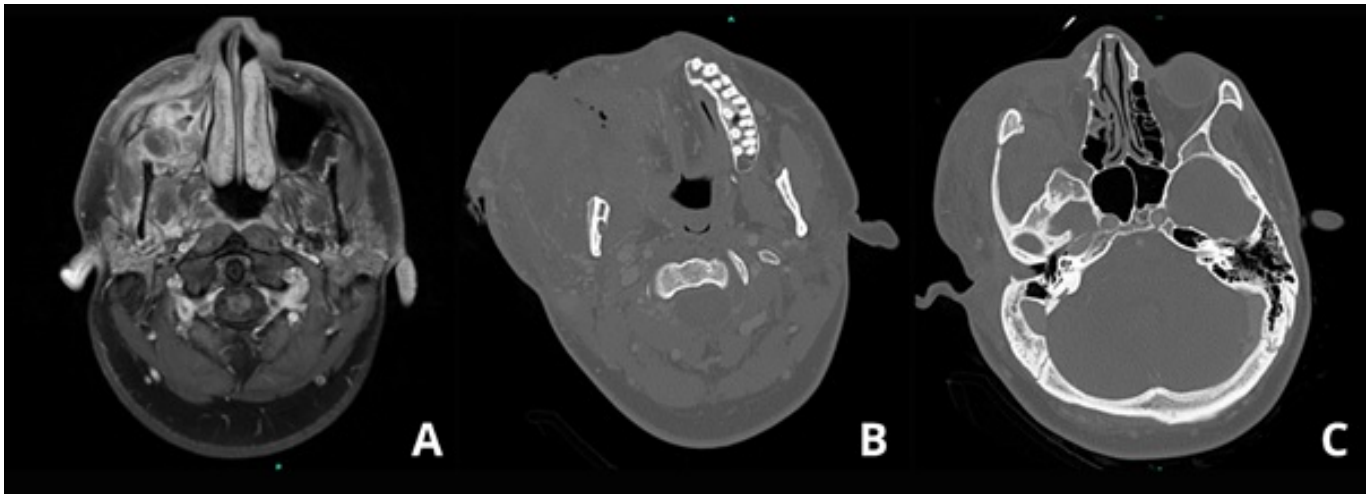

Figure 3. (**A**) Magnetic resonance imaging of the skull, tumor area and soft tissue expansion on the right side. (**B**, **C**) Computed tomography of the skull, tumor expansion on the right side.

DISCUSSION

The oral cavity is the most common site for the development of SCC in the head and neck region of patients with Fanconi anemia. In the general population, the etiology of this tumor is usually linked to lifestyle habits, such as alcohol and tobacco consumption. However, in patients with FA, the cause remains unknown and is likely related to the chromosomal abnormalities and DNA repair defects characteristic of the syndrome[1,5].

This case highlights the aggressive behavior of oral cancer, characterized by the rapid emergence of

multiple lesions in different anatomical sites in a young patient with Fanconi anemia (FA). Hematopoietic cell transplantation, the only curative option for the hematological manifestations of FA, has been associated with an increased risk of malignant transformation[1,3,6,7]. Furthermore, the development of graft-versus-host disease (GVHD) is recognized as a condition that may predispose to oral potentially malignant disorders[8,9]. Taken together, these factors significantly elevate the risk of oral malignancies in patients with FA.

Studies have shown that the development of solid tumors in the head and neck region among patients with FA markedly diverges from the natural history observed in the general population. In FA patients, SCC often do not arise from identifiable potentially malignant disorders, tend to occur at younger ages, and exhibit rapid progression[1]. While in the general population the average onset is around 45 years[10], FA patients typically develop these tumors around the age of 20. One study compared the risk of SCC development between FA patients who underwent HCT and those who did not. The findings revealed that 50% of patients who underwent HCT developed SCC by the age of 29, whereas the same proportion of non-transplanted patients developed the disease by age 45[6]. In the present case, the first intraoral lesion diagnosed as SCC appeared 11 years after HCT, when the patient was 21 years old and had no history of deleterious habits- further supporting the data reported in the literature.

Preventive monitoring and early diagnosis of malignant lesions in the oral cavity of patients with Fanconi anemia (FA) present significant challenges. These individuals frequently develop a range of oral mucosal lesions — such as lichenoid reactions, graft-versus-host disease (GVHD), leukoplakias, and traumatic hyperkeratosis — which complicate clinical evaluation, management decisions and delay recognition of malignant transformation[11]. Additionally, the potential for malignancies to arise in multiple anatomical sites increases the risk of developing synchronous or metachronous tumors within the oral cavity[12].

Oral potentially malignant oral disorders (OPMDs), particularly oral leukoplakia as identified in the present case, represent a significant clinical challenge due to their unpredictable potential for transformation into SCC. Among patients with Fanconi anemia, oral leukoplakia is considered the most prevalent OPMD[13]. At the time of initial diagnosis, leukoplakia is typically identified by excluding other oral conditions, making it a provisional clinical diagnosis. Erythroleukoplakia, which was also observed in the present case, is classified as a subtype of non-homogeneous leukoplakia and carries a higher risk of malignant transformation. Definitive diagnosis of such lesions requires incisional biopsy, which can confirm or modify the clinical hypothesis[14,15].

As an alternative to conventional biopsies, exfoliative cytology has shown promising potential. This non-invasive technique allows for repeated monitoring and is particularly useful in high-risk individuals, such as FA patients, who frequently present with multiple lesions. In a cohort study, approximately 63% of participants with FA exhibited lesions in early stages of malignancy, reinforcing the value of exfoliative cytology as a screening tool. However, this method does not yet replace traditional biopsy and requires further research and validation[15].

Recent updates in the management of oral leukoplakia suggest a personalized approach based on lesion risk stratification, focusing on preventing malignant transformation and implementing therapeutic interventions when necessary. In extensive lesions, it is recommended to perform biopsies at multiple sites to avoid underdiagnosis. For moderate to severe dysplasia, surgical excision — either by conventional techniques or laser — is indicated, whereas low-risk lesions should be monitored closely through regular clinical follow-up. Adjuvant strategies such as topical or systemic chemoprevention are under investigation, although specific data on their efficacy in FA patients remain unavailable[15].

In parallel with diagnostic and therapeutic innovations, the training of dental surgeons in the early identification of oral lesions is of great importance, particularly in remote areas far from specialized care centers. In this context, teledentistry emerges as a strategic tool to overcome geographic barriers and reduce the incidence of late-stage diagnoses of oral cancer, a factor directly related to patient prognosis[16].

In the clinical case presented, the patient exhibited leukoplastic lesions in various regions, including the hard palate. These lesions were evaluated using complementary exams such as biopsies and exfoliative cytology and were associated with recurrent fungal infections. However, regular monitoring was hindered by geographical barriers, as the patient lived in another state and had to travel periodically for specialized care. These logistical challenges, compounded by the rapid clinical progression of the disease, compromised continuous monitoring and early diagnosis.

Although OPMDs are common in FA patients, their absence does not eliminate the risk of developing oral

carcinoma. A systematic review indicates that malignant lesions may arise independently of prior OPMDs[12]. In the reported case, a lip lesion initially diagnosed as a chronic lichenoid-pattern lesion had been previously identified but not excised, and the patient was under clinical surveillance. The other malignant lesions emerged without any visible precursor lesions, underscoring the need for ongoing vigilance even in the absence of evident clinical signs.

In Fanconi anemia (FA), squamous cell carcinoma (SCC) is the most frequently diagnosed solid tumor, with the tongue and gingiva being the most common sites of development. Clinically, it may present as an ulcer with indurated borders, an exophytic lesion, or an erythroplakic or leukoplakic area, which can bleed upon manipulation and is typically painless in the early stages[17-19]. Histopathologically, it originates from dysplastic oral squamous epithelium and is characterized by islands and cords of malignant epithelial cells with varying degrees of differentiation, which may exhibit cellular pleomorphism, atypical mitoses, and keratin pearl formation in well-differentiated cases. The presence of perineural and vascular invasion, along with depth of invasion, are important prognostic factors[19,20]. Figure 4 shows two histopathological sections of squamous cell carcinomas.

Head and neck squamous cell carcinoma is generally treated with surgery, radiotherapy, chemotherapy, and, more recently, immunotherapy, with treatment selection tailored to the clinical and histopathological characteristics of each case. However, in patients with FA, these therapeutic approaches face significant limitations due to the syndrome's marked radiosensitivity and chemosensitivity. The literature reports a well-documented intolerance to chemotherapy — particularly alkylating agents — as well as to radiotherapy, with frequent occurrences of severe myelotoxicity[5,21,22].

Given these limitations, surgical resection with clear margins is established as the treatment of choice. However, surgical success is highly dependent on early diagnosis, as the presence of multifocal or recurrent tumors can significantly reduce curative potential. While surgery remains the preferred approach, radiotherapy and chemotherapy may still be considered on an individualized basis, particularly when surgery is contraindicated or in cases of unresectable tumors. Moreover, hesitation to administer adjuvant therapies — such as chemotherapy or radiotherapy — may result in high recurrence rates[5,21,22].

In this context, clinical management must be carefully planned to balance oncologic efficacy, toxicity minimization, and preservation of quality of life. Immunotherapy, although still underexplored in patients with Fanconi anemia, has been considered a promising alternative. In a cohort study, FA patients who received immune checkpoint inhibitors did not experience direct treatment-related complications; however, they developed secondary malignancies or other complications that led to poor outcomes, highlighting the need for further research to evaluate the safety and efficacy of this approach in this specific population[22].

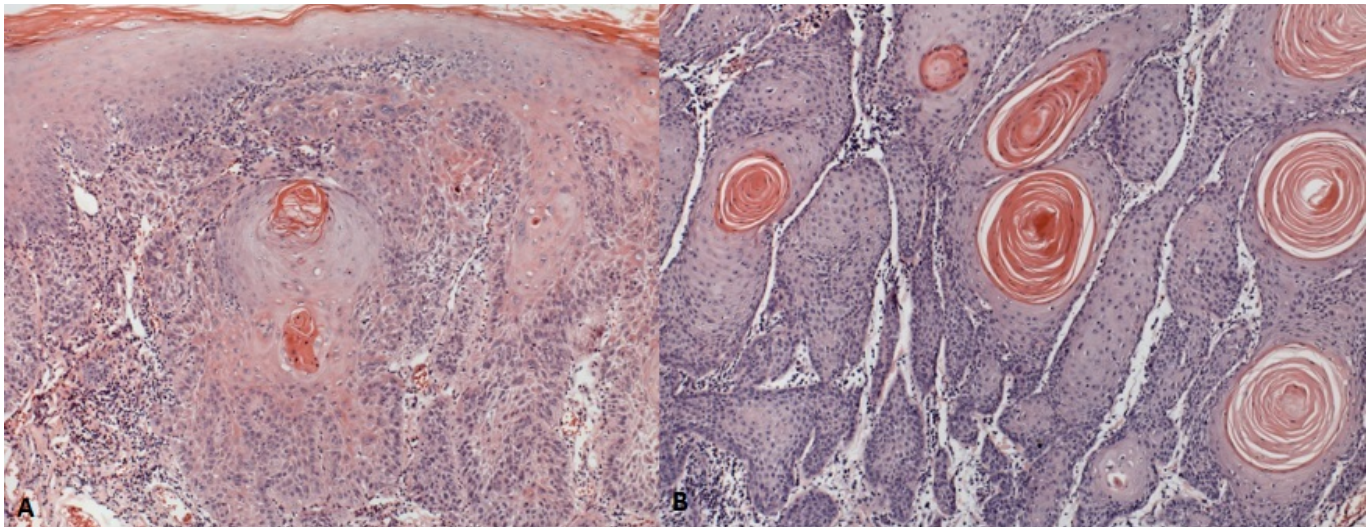

Figure 4. Oral Squamous cell carcinomas. (**A**) Histological section showing a lymphoplasmacytic inflammatory infiltrate attempting to control tumor invasion; cords of dysplastic epithelial cells infiltrating the connective tissue, with the formation of a keratin pearl. (**B**) Histological section at higher magnification showing infiltrative proliferation of dysplastic epithelial cells, arranged in cords and nests invading the underlying connective tissue; marked keratinization within the tumor nests, forming multiple well-developed keratin pearls, a characteristic feature of well-differentiated OSCC.

In the reported case, the patient underwent multiple complete surgical resections with histologically clear margins. Nevertheless, new aggressive lesions rapidly emerged. Access to comprehensive healthcare services and the patient's poor performance status precluded further systemic therapy. Following the identification of an inoperable tumor, the medical team transitioned to palliative care.

Unlike the general population — where SCC most frequently affects the tongue and floor of the mouth — patients with FA do not exhibit consistent anatomical predilections for malignant transformation[3,4]. This results in a broad cancerization field and a higher likelihood of multifocal disease. In this case, distinct lesions were identified in contiguous oral sites, such as the lower lip and right alveolar ridge, with rapid invasion into the right maxillary sinus, sphenoid wing, and orbital floor. This pattern likely reflects the persistence of pre-neoplastic fields harboring genetically unstable cells. Even after treatment, these altered fields can give rise to local recurrences and second primary tumors, significantly increasing mortality risk[23,24].

In addition, patients with Fanconi anemia (FA) are at increased risk for the development of second primary tumors. In a retrospective cohort, approximately 27.3% of patients developed new malignancies, including head and neck squamous cell carcinomas, as well as breast, lung, skin, and liver cancers. The time interval for the emergence of these tumors varied widely among cases, underscoring the need for long-term surveillance even after remission of the initial tumor[22]. The persistence of altered fields promotes not only local recurrences but also the formation of new malignancies, significantly impacting prognosis and long-term survival[24,25].

Although genetic predisposition remains the primary driver of solid tumor development in FA, hematopoietic treatments such as HCT also contribute significantly to carcinogenic risk. This dual vulnerability underscores the importance of early, multidisciplinary strategies that not only aim to improve survival but also prioritize quality of life[26]. Educating patients and families about oral cancer risks and ensuring regular follow-up with oral medicine or oncology specialists are essential for effective surveillance[1].

Thorough examination of the oral mucosa, strategic biopsies and exfoliative cytology of multiple sites, and the surgical removal of suspicious lesions can aid in clinical control but do not eliminate the risk of SCC development. A deeper understanding of field cancerization and prevention strategies remains an unmet need, particularly due to the rarity of FA. Standardizing oral surveillance protocols based on predefined risk criteria could support healthcare teams in recognizing early signs of malignancy, potentially reducing diagnostic delays[12,25,27]. Finally, although preventive and diagnostic strategies are under development, the prognosis for patients with FA who develop SCC remains guarded. Optimal management requires an individualized approach focused on minimizing treatment-related toxicity while aiming for satisfactory oncologic outcomes.

CONCLUSION

This case underscores the complexity of managing malignant lesions in patients with FA, highlighting the urgent need for continuous monitoring of oral lesions, as well as a comprehensive understanding of field cancerization. Improving prognosis, increasing survival rates, and enhancing quality of life in this population depend on early diagnosis, timely intervention, and the implementation of individualized treatment strategies tailored to the unique clinical challenges presented by FA.

AUTHORS' CONTRIBUTIONS

CALR: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. WTK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. PQMS: Conceptualization, Methodology, Validation, Visualization, Writing – original draft. AMG: Conceptualization, Methodology, Validation, Visualization, Writing – original draft. JLS: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

CONFLICT OF INTEREST STATEMENT

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: Not applicable.

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