Case Report

Management of oral leukoplakia in patients with Fanconi anemia

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Abstract

Fanconi anemia (FA) is a rare genetic disease involving an increased risk of developing acute myeloid leukemia and solid tumors, especially head-and-neck squamous cell carcinomas, for which the oral cavity is the most frequent site of occurrence. The patient presented in this study underwent allogeneic hematopoietic stem cell transplantation (HSCT) and developed nonhomogeneous oral leukoplakia after 7 years, which was promptly removed and diagnosed with high-grade epithelial dysplasia. Many risk conditions for oral squamous cell carcinoma were featured in the present case including FA, allogeneic HSCT, graft-versus-host disease, immunosuppressive therapy, female gender, nonsmoker, tongue location and nonhomogeneous type of leukoplakia. Close follow-up of the entire upper aerodigestive tract mucosa and early removal of all suspected lesions are highly recommended in the management of such patients.

Keywords: Allogeneic hematopoietic stem cell transplantation, epithelial dysplasia, excisional biopsy, oral squamous cell carcinoma, risk factors

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Submitted: 06-Aug-2021, **Accepted:** 05-Sep-2021, **Published:** 28-Feb-2022

INTRODUCTION

Fanconi anemia (FA) is a rare genetic disease with autosomal or X-linked recessive transmission, with a prevalence at birth of about 1:160000 and a frequency of disease gene carriers higher than 1:200. The FA male/female ratio is approximately 1.2:1.0 and the average age at diagnosis is 7 years.[1] The complete form of FA [Table 1][2,3] is clinically characterized by congenital abnormalities, birth defects, growth retardation, progressive bone marrow failure and increased risk of developing acute myeloid leukemia and solid tumors,[4,5] especially head-and-neck squamous cell carcinoma (HNSCC),[2] for which the oral cavity is the most frequent site of occurrence.[6]

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/jomfp.jomfp_280_21

Biallelic mutation (or even monoallelic in the case of FANCR/RAD51) of 23 genes has been identified as being responsible for FA.[7] These genes encode proteins with a repair mechanism role in DNA, in particular the stability of replication forks and DNA interstrand crosslink repair,[8-10] and in maintaining genome stability, such as in the correct segregation of chromosomes during cytokinesis.[11] Such alterations favor genome instability and tumorigenesis.[12,13]

Not all FA patients present all clinical alterations, and malformations may not be present, so that diagnosis is reached at a later age when bone marrow failure or

How to cite this article: Pippi R, Di Gioia C, La Rocca U, Bellisario A, Iori AP. Management of oral leukoplakia in patients with Fanconi anemia. J Oral Maxillofac Pathol 2022;26:S133-8.

Table 1: Clinical alterations possibly present in patients with Fanconi anemia

Short stature
Hyperpigmentation of the skin
Abnormalities of gastrointestinal, genital and urinary tract
Bone changes, including hypoplasia or absence of the thumbs or radius
Infertility
Progressive bone marrow failure
High risk of leukemia
High risk of solid tumors, especially head-and-neck squamous cell carcinoma

solid cancer in young subjects usually develops,[14] based on the search for chromosomal breakages induced by diepoxybutane (DEB) or mitomycin C.[15,16] Allogeneic hematopoietic stem cell transplantation (HSCT) is curative for bone marrow failure in patients with FA, but the cancer development, including oral cancer, is associated with a poor prognosis and the management of these patients is still challenging.[17-19]

CASE REPORT

A 41-year-old female patient was referred to the Oral and Maxillofacial Sciences Department, "Sapienza" University of Rome, in October 2019 for a whitish area of the tongue. In August 2000, the patient was diagnosed with bone marrow aplasia and therefore underwent immunosuppressive therapy with cyclosporine and prednisone, with a good clinical response. In 2003, due to the presence of thrombocytopenia and the worsening of anemia and neutropenia, she received immunosuppressive therapy with horse antilymphocyte serum, prednisone and cyclosporine. In 2005, the patient was treated with erythropoietin due to persistent anemia. In 2007, the patient repeated a DEB test at the Hematology Department at "Sapienza" University of Rome which resulted positive, therefore, she was diagnosed with FA. Since there was no HLA identical match in her family, a search for an unrelated volunteer donor began without success. In 2012, the cytogenetic analysis of bone marrow aspiration showed a chromosome 8 trisomy. Finally, in June 2012, an unrelated HLA compatible donor was found, and in August 2012, due to persistent pancytopenia and cytogenetic alteration, the patient underwent a HSCT. The pretransplant conditioning involved the use of cyclophosphamide and fludarabine, while for graft-versus-host disease (GVHD), prophylaxis, mycophenolate, cyclosporine and antilymphocyte serum were used.

Thirty days after HSCT, the patient developed a cutaneous Grade II GVHD, treated with steroid therapy, with gradual improvement until disappearance of clinical manifestations.

In 2014, the patient developed joint inflammatory arthropathy of the lower limbs and again underwent immunosuppressive therapy with resolution of clinical symptomatology.

For the following years, the patient was periodically followed by the transplant team for oral mucosal evaluation until October 2019 when she was referred for consultation.

During the first examination at the Oral and Maxillofacial Sciences Department, a symptomless 1-cm white lesion with a small, central erosive area [Figure 1] was noticed on the left margin of the tongue. Selective grinding of lingual cusps of third quadrant teeth was carried out twice during the next 4 weeks to smooth out any sharp edges that could traumatize the mucosa of the left lingual margin. The patient's medical history did not include any flawed habits or the use of voluptuous substances, such as alcohol or tobacco, and no induration was present on palpation.

Since no clinical improvement occurred and the anteroposterior diameter of the lesion remained unchanged [Figure 2], an excisional biopsy of the lesion was performed with sutures for specimen orientation [Figure 3]. The surgical sample was fixed with 10% formalin and embedded in paraffin for microscopic evaluation of H&E-stained sections (3 μm).

The histopathological picture showed an ulcerated keratotic lesion of the lingual mucosa with focal high-grade epithelial dysplasia; the lesion was completely excised with negative surgical margins [Figures 4 and 5]. The patient then underwent weekly follow-up sessions, until healing was complete [Figure 6].

In July 2020, a whitish area on the left floor of the mouth and two white lesions, one on the buccal interdental papillae between the upper right premolars and one distal to the first molar, were found.

During the last follow-up examination (December 16, 2020), persistence of the previously identified lesions was observed, although they appeared to be less evident and not related to traumatic chewing or brushing. Therefore, the patient has been included in a monitoring program with more frequent visits than the previous.

DISCUSSION

Conventionally, the development of oral squamous cell carcinoma is associated with risk factors such as tobacco and alcohol consumption, but their use is less frequently reported in patients with FA than in the general

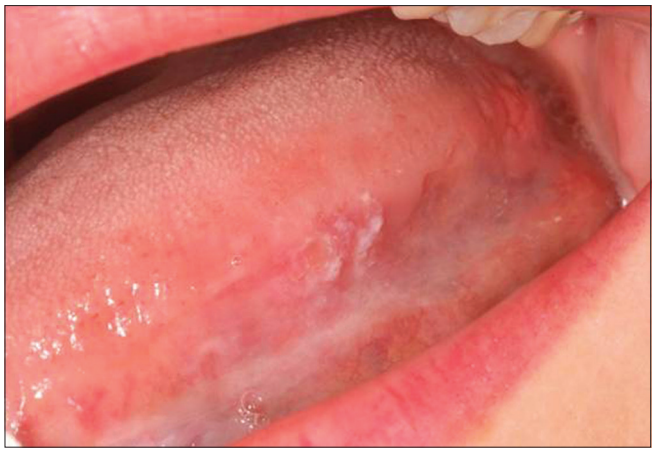

Figure 1: Nonhomogeneous leukoplakia with a central erosive area on the left lingual margin

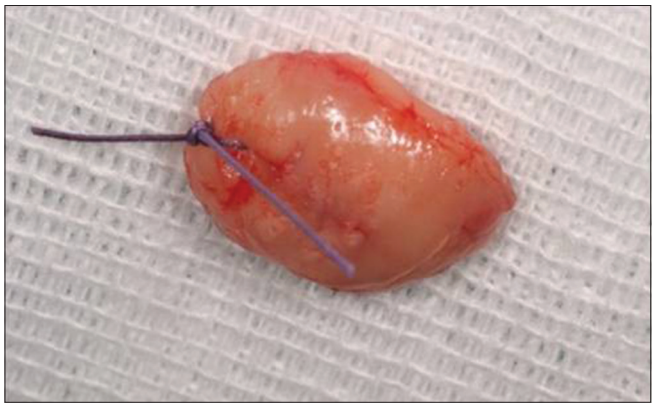

Figure 3: Excisional biopsy: Sample orientation with a suture knot on the anterior margin

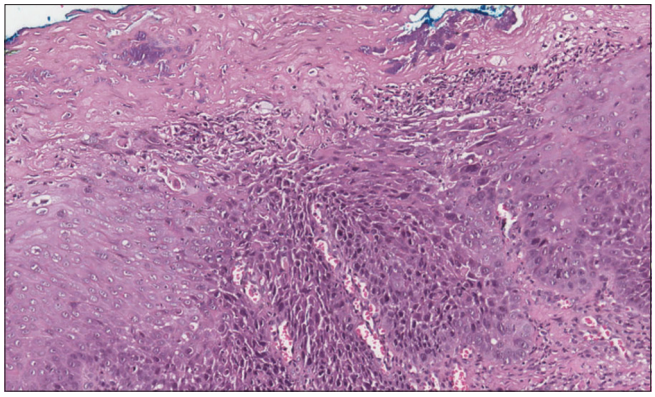

Figure 5: Detail of Figure 4 with focal high-grade epithelial dysplasia (×10). Hematoxylin and eosin staining

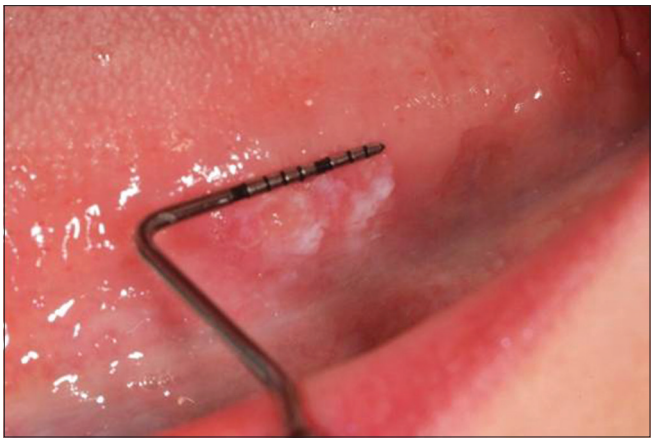

Figure 2: Lesion measurement with a periodontal probe

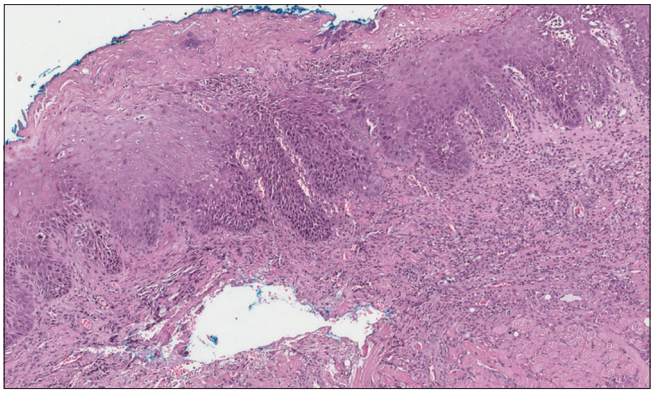

Figure 4: Tongue mucosa showing an ulcerated keratotic lesion (×4). Hematoxylin and eosin staining

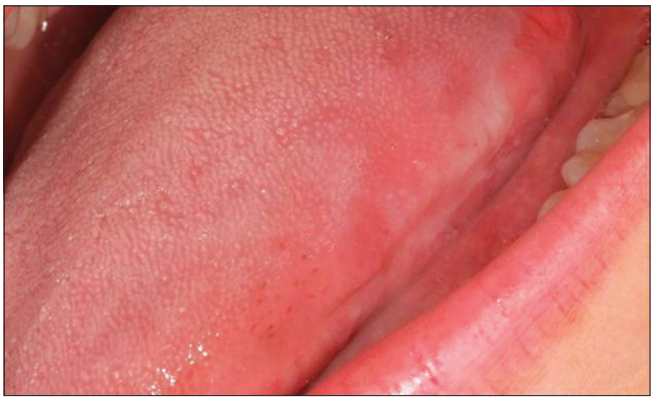

Figure 6: Complete healing 1 month after biopsy

population.[14] However, tobacco and alcohol are major risk factors for HNSCC in FA patients as well, thus discouraging their consumption is always necessary.[14] In addition, oral cancer is usually more frequently found in males over 45, whereas in FA patients, it is diagnosed at a median age of 26.5 years, more frequently involving females and the tongue location (about 60% of cases).[20]

Reasons for this increased susceptibility of oral mucosa to develop cancer can be partly ascribed to the concept of field cancerization,[21] which concerns the exposure to a harmful environment over a lengthy period. However, the genomic instability related to FA and possibly to HSCT, rather than the chronic exposure of the entire upper aerodigestive tract to exogenous factors, including tobacco and alcohol, may play the greatest role in the present case. Cancer stem cells are possibly involved as well, since they

have been recently considered to have an important role in HNSCC development, both in tumor initiation and progression.[22] Furthermore, human papillomavirus (HPV) has been found to be associated with oral and especially with oropharyngeal SCC, although the present patient did not undergo specific investigations for HPV DNA in oral mucosal cells or for serum mRNA antibodies.[23] Finally, potentially malignant oral disorders, and especially nonhomogeneous leukoplakia, represent a further risk of cancerization.[24]

Patients with FA have a 500–700-fold higher risk of developing HNSCC than the general population,[25] and in about two-thirds of cases, cancer occurs in the oral cavity.[17]

Allogeneic HSCT has also been found to increase the risk of developing solid tumors,[26,27] with a rate of 2%–6% at 10 years and 6%–13% at 15 years,[28,29] with oral squamous cell carcinoma (OSCC) representing approximately 50% of all cases.[30]

In 2003, Alter *et al*. found that all FA subjects undergoing bone marrow transplantation developed oral cancers (12/12) and were younger than oral cancer FA patients not undergoing HSCT (21 and 28 years, respectively).[4]

In 2011, Mawardi *et al*. performed a retrospective study on 26 patients undergoing allogeneic HSCT and who developed oral dysplasia (8 patients) and OSCC (18 patients) in an average time of 2.5 and 8 years after HSCT, respectively.[31]

In 1997, Curtis *et al*. analyzed 19,229 patients undergoing allogeneic (97.2%) or syngeneic (2.8%) HSCT and found a significantly higher risk of developing new solid tumors than in the general population, including oral cancers. Furthermore, the risk increased with increasing time from transplantation and in males. Finally, the onset of GVHD was strongly associated with increased risk for skin or mouth SCC.[28]

In a 2016 case–control study, 183 patients with solid cancers (58 – SCC and 125 – non-SCC) after transplantation and 501 controls were included in a cohort of 24,011 patients who underwent HSCT at 215 worldwide centers. A close correlation was found between the risk of SCC and both chronic GVHD and its therapy. A long duration of therapy for GVHD, severe chronic GVHD and use of azathioprine, especially when combined with steroids and cyclosporine, were found to be major risk factors for the development of SCC.[32] In the present case, the patient, despite not having developed oral GVHD, presented a second-degree skin GVHD, treated with steroids, and she underwent treatment with cyclosporine for many years. Curtis *et al*. pointed out that prolonged immunosuppressive therapy, especially in the case of azathioprine, is significantly associated with the risk of SCC of the skin and oral mucosa.[32]

The management of the present case was in line with the high risk of oral mucosa cancerization. Once the lesion was identified, factors possibly responsible for any chronic irritation of the tongue mucosa were initially removed. Since there was no clinical improvement, a biopsy was scheduled. An excisional biopsy, rather than incisional biopsy, with full-thickness removal of the mucous layer, was performed due to the benign, clinical appearance and the small size of the lesion.[33] Biopsy specimen orientation was nevertheless carried out to be able to intervene again on the right side of the surgical wound in the case of incomplete excision of pathological tissue.[33] Histopathological diagnosis complies with the grading systems for epithelial dysplasia proposed by the 2017 World Health Organization classification of head-and-neck tumors.[34] Case management is in line with the 2008 flowchart, proposed by van der Waal,[35] which provides for excision of all leukoplakias, regardless of the presence of dysplasia. This means that a previous incisional biopsy is not necessary to program the complete removal of small leukoplakias unless surgery does not lead to postoperative functional or/and esthetic defects.[33] This kind of approach is exceedingly important if many risk factors for malignant transformation are simultaneously present. In the present case, besides epithelial dysplasia, FA, HSCT and GVHD, several risk factors for malignant transformation of leukoplakia were present, among those reported having statistical significance, such as female gender, nonsmoker status, tongue location and nonhomogeneous type of leukoplakia,[35] although the direct progression from such lesions to oral cancer has not yet been demonstrated.[24] Although it is still unknown whether complete removal of leukoplakia really prevents the occurrence of oral SCC in a certain site, close follow-up examinations and early diagnosis and removal of all suspected lesions are of paramount importance in preventing oral SCC in high-risk patients for several reasons. First, in FA patients, more than one oropharyngeal tumor often develops and is not only synchronous but also metachronous.[36] Second, since among all treatment strategies for advanced stage SCC, radiotherapy and chemotherapy must be avoided in FA patients due to a high risk of severe, sometimes fatal toxicity,[37,38] whether on the one hand, demolition surgery is the only therapeutic weapon in the case of late diagnosis, on the other hand, an early surgical approach to treat both micro-infiltrative and initial oral SCCs or potentially malignant lesions, including leukoplakia and erythroplakia,

seems to be the only prognostically valid treatment option. Finally, as for the residual whitish areas, they fall under the concept of field cancerization and epithelial development instability typical of both FA and HNSCC and must therefore be closely monitored and possibly removed when persistent, regardless of their clinical appearance.

CONCLUSIONS

Patients with FA should be closely followed to be able to detect any oral mucosal alterations early, since they may develop into cancer or already be cancer. Susceptibility of these patients to oral cancer development greatly increases in relation to factors such as allogeneic HSCT treatment, GVHD onset, duration and severity and duration of immunosuppressive therapy. Field cancerization may be another reason for an increased risk of cancer occurrence in the entire upper aerodigestive tract so that both continuous follow-up and removal of all other risk factors for oral cancer are necessary for the rest of the patient's life. Early surgical removal of all suspected lesions is necessary as well.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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