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Short Communication

The onset and progression of oral potentially malignant disorders in Fanconi anemia patients: Highlighting early detection of oral cancer

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Abstract In 2020, Fanconi anemia (FA) was classified as a syndrome with insufficient epidemiological evidence in the oral potentially malignant disorder (OPMD) group by the WHO Collaborating Centre. The paucity of case reports on FA-associated OPMD limits evidence-based management, and such cases have not been analyzed collectively in detail. Hence, the objective of this short communication is to summarize the evidence on the onset and progression of OPMD in FA patients, so as to better understand the natural history of oral cancer development in patients affected by FA. A total of 11 eligible papers containing 1332 FA patients are involved in onset and progression of OPMD in FA patients. Of these, 186 (14.0%) were diagnosed with OPMD. With available data from 4 follow-up studies, 30 (41.1%) of 73 FA patients compatible with OPMD further developed into OSCC at young age (10–30 years old). The evidence on FA with malignant potential comprise clinical epidemiology, oral cytology

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abnormalities, DNA aneuploidy, loss of autofluorescence, loss of heterozygosity, high-risk human papillomavirus infection, DNA mutations in saliva and plasma samples. Collectively, these can consummate the evidence on FA as a syndrome that may potentiate cancer development in oral cavity mentioned by the WHO. Importantly, it highlights close surveillance is instrumental for FA patients with OPMD to early detect oral cancer.

Introduction

Fanconi anemia (FA) is a rare inherited disease of genomic instability that may lead to bone marrow failure, hematologic and solid malignancies, mainly head and neck cancers.[1] Hematopoietic stem cell transplantation (HSCT) is the only curative therapeutic option for this feature of the disease.[2] Due to better survival rates from successful HSCT, many patients with FA now are surviving into adulthood even though with the risk of chronic graft-versus-host disease (GVHD).[2,3] After HSCT, however, patients with FA have a greater than 500-fold incidence of head and neck squamous cell carcinoma (HNSCC) relative to the general population, with over two-thirds of cases being oral squamous cell carcinoma (OSCC) at young ages.[2,3] Early detection of FA-associated OSCC allows for treatment with surgery only, conferring the highest chance of survival, as well as the potential to avoid radiation and chemotherapy treatments.[2,3] Theoretically, FA-associated OSCCs are typically preceded by potentially malignant visible lesions in the oral cavity; whereas they frequently present at advanced stages with correspondingly poor survival.[2—4] Besides, the investigations on the precursors of OSCC in FA patients are seemingly insufficient.

In 2020, the World Health Organization (WHO) Collaborating Centre for Oral Cancer presented a consensus report from an international seminar on nomenclature and classification of oral potentially malignant disorders (OPMD).[5] In the consensus report, FA that may potentiate cancer development in oral cavity was classified as a disorder with insufficient epidemiological evidence, and was not recommended for inclusion within the potentially malignant group of disorders.[5] Although a short description with emphasis on FA and head and neck cancer risk was provided, only one study on 16 cases diagnosed with oral leukoplakia in a group of Brazilian patients with FA was mentioned in the report.[5] The paucity of case reports on FA-associated OPMD limits evidence-based management, and such cases have not been analyzed collectively in detail. Most dentists have little personal experience with FA-associated OPMD, and a review is intended as a comprehensive resource for clinicians. In this context, the objective of this short communication is to summarize the evidence on the onset and progression of OPMD in FA patients, so as to better understand the natural history of oral cancer development in patients affected by FA.

Materials and methods

As per the methodology described previously,[4] we conducted a systematic literature search regarding the papers on OPMD and FA on 01 Apr 2023 from PubMed and Medline databases. According to the search strategy described in Supplementary Table S1, we used medical subject term "Fanconi anemia" in the title and "oral potentially malignant disorder" and its synonyms in all fields. Inclusion criteria were limited to case report, case series, and clinical research describing patients with OPMD and Fanconi anemia. Exclusion criteria were literature reviews, experimental (animal and cell line) studies, patients reported in previous publications, and publications that did not report the visible lesions at oral sites. There was no restriction to language and year of publication, and an additional query was performed in the reference list. Titles and abstracts or full texts of the articles were screened and re-evaluated to confirm the eligible papers. Data search and extraction were undertaken independently by two investigators (Y.L. and W.L.), and any disagreement was resolved in a consensus symposium. The bibliographical characteristics of all the eligible articles were reviewed and recorded the following information: authorship, publication year, country/region of origin, title, study design, number of patients, and main results. Descriptive statistics and associations were calculated for these characteristics.

Results

The onset and progression of OPMD in FA patients

As presented in Table 1, there were 11 eligible papers containing 1 retrospective study, 2 case reports, 4 cross-section studies, and 4 follow-up studies involved in OPMD onset in FA patients.[6—16] A total of 1332 patients with FA from 7 countries (France, Brazil, Italy, United States, Netherlands, Germany, and Spain) are identified in literature. Among 1332 FA patients, 186 (14.0%) were diagnosed with OPMD. With available data from 4 follow-up studies, 30 (41.1%) of 73 FA patients compatible with OPMD further developed into OSCC at the young age (10—30 years old). The evidence on FA with malignant potential comprise clinical epidemiology, oral cytology abnormalities, DNA aneuploidy, loss of autofluorescence, loss of heterozygosity

Table 1 Summary of included studies focusing on Fanconi anemia (FA) patients diagnosed with OPMD.

Author, year	Country	No. of FA patients	No. of HSCT	Smoking/ drinking (%)	Median age (range, y)	Study design	Mean follow-up (m)	No. of case diagnosing OPMD (%)	No. of case developing OSCC (%)	Sample	Main results
Masserot et al. 2008[6]	France	13	13 (100%)	No	9.7 (4.5—19.2)	Retrospective	NA	9 (69.2%)	NA	NA	69.2% patients who had undergone HSCT had oral premalignant lesions before the diagnosis of HNSCC
Resende et al. 2011[7]	Brazil	1	1	No	8	Case report	24	1	NA	Tissue	A case of oral "recurrent" leukoplakia in a FA patient after HSCT and loss of heterozygosity (LOH) in the first lesion.
Pippi et al. 2022[8]	Italy	1	1	No	41	Case report	NA	1	NA	NA	A nonsmoker female case developed nonhomogeneous leukoplakia after HSCT 7 years
Grein et al. 2015[9]	Brazil	138	0	NA	9 (1—38)	Cross-section	NA	16 (11.6%)	NA	NA	16 FA patients (11.6%) without HSCT were diagnosed with oral leukoplakia
Grein et al. 2015[10]	Brazil	96	96 (100%)	NA	16 (5—42)	Cross-section	NA	40 (41.7%)	NA	NA	40 FA patients (41.7%) presented with oral manifestations compatible with GVHD.
Abram et al. 2018[11]	United States	59	33 (55.9%)	13.6%/67.8%	58	Cross-section	NA	37 (63.8%)	NA	Brush	Loss of autofluorescence coupled with quantitative cytology aids in distinguishing high- and low-risk OPMD in FA patients.
Portugal et al. 2019[12]	Brazil	49	33 (67.3%)	16.3%/30.6%	20 (5—44)	Cross-section	NA	10 (20.4%)	NA	Swab	Multiple HPV types were detected in 78% and 71% of HPV samples by Sanger sequencing and reverse hybridization methods, respectively.

Smetsers et al. 2015[13]	Netherlands	141	0	7.8%/19.9%	11.1 (2.7—52.3)	Follow-up	66.1 (0—93.7)	28 (19.9%)	5 (3.5%)	Brush	The prevalence (9.9%) of LOH, mainly at 9p in brushed samples of the oral epithelium of FA patients.
Velleuer et al. 2020[14]	Germany	713	504 (70.7%)	NA	27.3 (7.3—55.3)	Follow-up	48 (0—149)	30 (4.2%; high-grade dysplasia)	19 (2.7%)	Brush	Oral cytology (with a sensitivity of 97.7% and a sensitivity of 84.5%) and DNA ploidy (100% and 92.2%) to determine oral (pre)cancer
Archibald et al. 2022[15]	United States	105	95 (90.5%)	NA	11.3 (1.6—31.6)	Follow-up	63 (<1—161)	9 (8.6%)	4 (3.8%)	NA	8.6% of patients had leukoplakia or erythroplakia and 3.8% developed malignancy.
Errazquin et al. 2023[16]	Spain	16	11 (68.8%)	NA	27 (14—46)	Follow-up	24 (15—37)	6 (37.5%)	2 (12.5%)	Saliva & plasma	9/16 FA patients had mutations in at least one liquid biopsy sample; all of them displayed OPMD/OSCC afterwards; 7/16 patients displayed no mutations, 6 of whom were free of OPML/OSCC.

HPV, human papillomavirus; HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease; NA, not available; OPMD, oral potentially malignant disorders; OSCC, oral squamous cell carcinoma.

(LOH), high-risk human papillomavirus (HPV) infection, DNA mutations in liquid biopsy (saliva and plasma) samples.

Natural history of OSCC development in FA patients

Beddok and colleagues recently reviewed the characteristics of the 4 main cohorts of FA patients with solid tumors, and there were 53 (2.2%) of 2381 FA patients developed into HNSCC, with OSCC being the most common type.[3] Lee and colleagues recently identified 91 FA-associated OSCC patients treated with surgery, radiotherapy, and/or systemic agents.[2] Furquim and colleagues identified 121 cases of FA-associated OSCC, which was the largest sample size in the review articles.[4] However, these papers did not highlight the precursors of OSCC in FA patients. We observed that 30 (3.1%) of 975 FA patients developed into OSCC based on 4 follow-up studies, and the 30 (41.1%) OSCC patients originated from 73 FA patients compatible with OPMD. Accordingly, natural history of OSCC development in FA patients should derive not only from oral mucosa without visible abnormalities but also from OPMD with visible lesions (Fig. 1). Also, it's entirely possible that FA-associated OSCC from OPMD are underestimated due to neglection and delayed diagnosis.

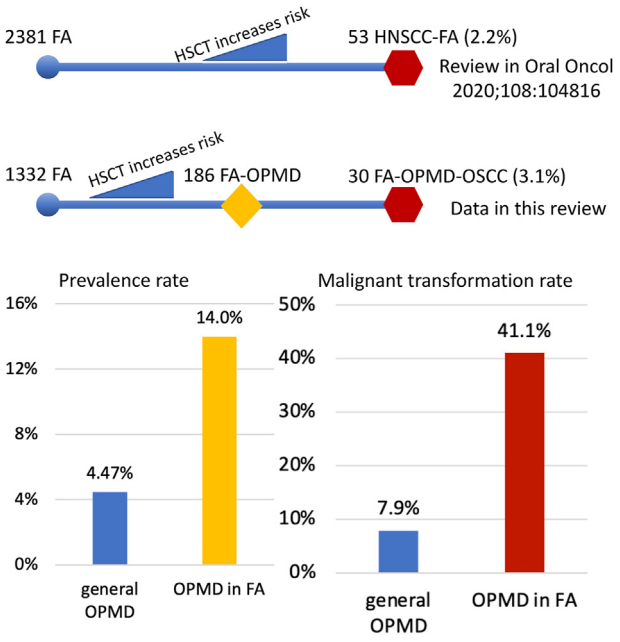

Figure 1 Natural history of oral squamous cell carcinoma (OSCC) development in Fanconi anemia (FA) patients. Among 1332 FA patients, 186 (14.0%) were diagnosed with oral potentially malignant disorders (OPMD). With available data from 4 follow-up studies, 30 (41.1%) of 73 FA patients compatible with OPMD further developed into OSCC. Overall prevalence (4.47%) of OPMD worldwide and malignant transformation rate (7.9%) of OPMD reported by systematic review and meta-analyses.[17,18] The risk of OSCC/OPMD onset in FA patients who received hematopoietic stem cell transplantation (HSCT) was increased compared to the patients without HSCT.

Discussion

In 2020, FA with insufficient evidence was not recommended for inclusion within the potentially malignant group of disorders by the WHO Collaborating Centre.[5] Apart from one study including 16 FA patients with oral leukoplakia from Brazil, we herein add 10 studies including 186 FA patients diagnosed with oral potentially malignant visible lesions.[6–16] We pool the incidence of OPMD onset in FA patients being 14.0%, which is obviously higher than overall prevalence (4.47%) of OPMD worldwide reported by systematic review and meta-analysis.[17] Further, we synthesize the rate of malignant transformation in FA patients with OPMD being 41.1%, which is also dramatically higher than overall rate (7.9%) of OPMD malignant transformation reported by systematic review and meta-analysis (Table 1).[18] Although these studies may be of some limitations, these still can consummate the evidence on FA as a syndrome that may potentiate cancer development in oral cavity mentioned by the WHO.[5]

The evidence on FA with malignant potential comprise clinical epidemiology, oral cytology abnormalities, DNA aneuploidy, loss of autofluorescence, LOH, high-risk HPV infection, DNA mutations. A retrospective study from France described that 9 (69.2%) of 13 FA patients who had undergone HSCT had oral premalignant lesions before the diagnosis of HNSCC, which was compatible with GVHD.[6] The authors from Brazil described that 16 (11.6%) of 138 FA patients who had not undergone HSCT had oral leukoplakia in a cross-section study;[7] Meanwhile, they described that 40 (41.7%) of 96 FA patients who had undergone HSCT had oral visible abnormalities in another cross-section study,[8] which was also compatible with GVHD. Basically, the association between HNSCC and FA syndrome, especially after HSCT, is established. The relative risk of HNSCC in FA patients who received HSCT is estimated to 4.4-fold compared with FA patients without HSCT have half of this risk.[4] The cases of OSCC in HSCT patients often occur within a shorter period or younger age than non-HSCT ones, in particular after 5 years after HSCT mainly owing to GVHD.[4]

Oral lesions in FA are clinically challenging, because they frequently involve large areas and appear multiple visible oral lesions. The treatment strategies of patients with FA, especially those who have undergone HSCT and present multifocally with that cannot all be biopsied, are very limited. An important challenge faced by clinicians managing FA patients with OPMDs is to be able to identify the proportion of patients most likely to develop a future OSCC. Thus, there is an urgent clinical need for alternative screening strategies with which to characterize high-risk premalignant cells. Due to close and repeated examination, noninvasive diagnostic technologies would be desirable as tissue biopsies are a burden for FA patient. Accordingly, the brushed or swabbed samples of the oral epithelium of FA patients were used to determine oral cytology abnormalities and in combined with DNA aneuploidy or autofluorescence, LOH, HPV infection, and saliva and plasma samples were used to determine gene mutations (Table 1 with adequate description).

Conventionally, tobacco and alcohol use are common risk factors for the development of OSCC; but their use are less frequently reported in FA patients than in the general population. Usually, oral cancer is more frequently diagnosed at over 45 years, whereas in FA patients with OPMD, it is

diagnosed common at young ages of less than 30 years. For OPMD patients with mild symptoms or unusual context such as no risk factors and younger age, it may be very useful for investigating mild anemia or unexplained findings that may unravel a yet undiagnosed FA. Collectively, it highlights close surveillance is instrumental for FA patients at pediatric ages, especially after HSCT. OPMD as art of the FA syndrome phenotype, should be informed of the significantly increased risks of malignant transformation and must therefore be closely monitored and possibly removed when persistent.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2023.06.001.

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