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Evaluation of inherited cancer syndromes with emphasis on Fanconi anemia classified as oral potentially malignant disorders

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Dear Editor,

According to a consensus report by the WHO Collaborating Centre for Oral Cancer in 2020[1], oral potentially malignant disorders (OPMDs) refer to a group of lesions and conditions characterized by a variably increased risk of developing cancers of the lip and the oral cavity. We read with great interest a correspondence entitled 'Bloom syndrome: an oral potentially malignant disorders aiding in malignancy vigour' recently published in the *International Journal of Surgery* by Muralidharan *et al*.[2]. We congratulate the authors for an interesting paper that provides insights to the association of Bloom syndrome as an inherited cancer syndrome with the risk of head and neck cancer susceptibility. Strikingly, the authors confidently classified Bloom syndrome as an OPMD in the paper title; however, they did not provide the relevant evidence. More importantly, the consensus report by the WHO classified inherited cancer syndromes, including Bloom syndrome and Fanconi anemia (FA), as disorders with insufficient epidemiological evidence[1]. Based on a literature search and to our knowledge, there may be evidence of Bloom syndrome associated with head and neck cancer risk, but lack of direct evidence on this disease associated with potentially malignant oral lesions. Hence, the authors could point out that the OPMD in the title was not supported by the paper text.

Inherited cancer syndromes carrying inherited genetic mutations in one or more genes predispose the affected individuals to the development of cancers, even in the absence of extrinsic risk factors such as tobacco or alcohol use[3]. The inherited genetic syndromes predisposing to head and neck cancer were previously reviewed with a comprehensive list, and important examples are FA, Bloom syndrome, Li Fraumeni syndrome, ataxia telangiectasia, and xeroderma pigmentosum[3–5]. However, their associations with head and neck cancer are poorly understood, probably due to the rarity of these diseases. In the current correspondence, we take the liberty of adding our thoughts on the association between inherited cancer syndromes and the risk and progression of OPMDs. To begin with, we conduct a literature review of PubMed and Web of Science databases of studies on this issue and confirm that a great majority of inherited cancer syndromes, including Bloom syndrome without epidemiological evidence, cannot be classified as OPMDs. As mentioned by the WHO Collaborating Centre in 2020[2], we also observe that FA still has stronger evidence for a predisposition for oral cancer compared to a dozen other inherited cancer syndromes.

FA is a rare inherited genetic condition that may lead to leukemia, bone marrow failure, and/or solid tumors, including head and neck cancers, with oral squamous cell carcinoma being the most common type at a relatively young age. As presented in Table 1, we then summarize the studies focusing on FA patients and the risk and progression of OPMDs with an adequate description. A total of nine studies[6–14] contained 1474 patients with FA from six countries identified in literature focused on OPMD research. Among 1474 FA patients, 182 (12.3%) are diagnosed with OPMD, mainly oral leukoplakia. In particular, 41.7% of patients with FA would present with oral manifestations after hematopoietic stem cell transplantation. With available data from four follow-up studies, 30 (41.1%) of 73 FA patients compatible with OPMD develop into OSCC at a young age (10–30 years old). The evidence on FA with malignant potential comprises clinical epidemiology, DNA mutations in saliva and plasma samples, oral cytology, DNA aneuploidy, chromosomal aneuploidy, high-risk human papillomavirus infection, loss of autofluorescence, and loss of heterozygosity.

HIGHLIGHTS

- There may be a lack of direct evidence on Bloom syndrome as an inherited cancer syndrome associated with oral potentially malignant disorders (OPMDs).
- Of inherited cancer syndromes, Fanconi anemia (FA) but not Bloom syndrome could be classified as an OPMD.
- For FA, the incidence of OPMD onset and progression to oral cancer is 12.3 and 41.1%, respectively.
- Our observations can consummate the evidence on FA in a consensus report by the WHO Collaborating Centre.

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Table 1

Summary of included studies focusing on Fanconi anemia (FA) patients with the diagnosis of oral potentially malignant disorders (OPMD), excluding case reports.

Evidence type	Country	Number of FA patients	Mean age (year)	Study design	Mean follow-up (m)	Number of cases diagnosing OPMD	Number of cases developing OSCC (%)	Sample	Main results	Reference
Clinical epidemiology	United States	105	11.3 (1.6–31.6)	Follow-up	63 (< 1–161)	9 (8.6)	4 (3.8)	–	The standardized incidence ratio of head and neck cancer was 483.8	Archibald *et al.*, 2022[6]
Clinical epidemiology	Brazil	96 with GVHD	16 (5–42)	Cross-section	NA	40 (41.7%)	NA	–	40 FA patients (41.7%) presented with oral manifestations compatible with GVHD	Grein *et al.*, 2015[7]
Clinical epidemiology	Brazil	138 without HSCT	9 (1–38)	Cross-section	NA	16 (11.6%)	NA	–	16 FA patients (11.6%) were diagnosed with oral leukoplakia	Grein *et al.*, 2015[8]
DNA mutations	Spain	16	27 (14–46)	Follow-up	24 (15–37)	6 (37.5)	2 (12.5)	Saliva and plasma	9/16 FA patients had mutations in at least one liquid biopsy sample; all of them displayed OPMD/OSCC afterward; 7/16 patients displayed no mutations, 6 of whom were free of OPMD/OSCC	Errazquin *et al.*, 2023[9]
Cytology	Germany	157	NA	Follow-up	NA	7 (high-grade dysplasia/OSCC)	Brush	Multicolor 9p21 chromosomal aneuploidy FISH assay in brush samples with a sensitivity of 87% and a specificity of 82.9% to determine oral (pre)cancer	Silva *et al.*, 2022[10]	
Cytology	Germany	713	27.3 (7.3–55.3)	Follow-up	48 (0–149)	30 (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	Velleuer *et al.*, 2020[11]
Cytology	Brazil	49	20 (5–44)	Cross-section	NA	9 (18.4)	NA	Swabs	Multiple HPV types were detected in 78% and 71% of HPV samples by Sanger sequencing and reverse hybridization methods, respectively	Portugal *et al.*, 2019[12]
Cytology	United States	59	58	Cross-section	NA	37 (63.8)	NA	Brush	Autofluorescence coupled with quantitative cytology aids in distinguishing high-risk and low-risk OPMD in FA patients	Abram *et al.*, 2018[13]
Cytology	Netherlands	141	11.1 (2.7–52.3)	Follow-up	66.1 (0–93.7)	28 (24%)	5 (3.5)	Brush	Loss of heterozygosity (LOH), mainly at 9p, was present in 14 (9.9%) nontransplanted patients with FA	Smetsers *et al.*, 2015[14]

FA, Fanconi anemia; FISH, fluorescence in situ hybridization; GVHD, graft-versus-host disease; HPV, human papillomavirus; HSCT, hematopoietic stem cell transplantation; NA, not available; OPMD, oral potentially malignant disorder; OSCC, oral squamous cell carcinoma.

These can consummate the evidence that FA could be classified as an OPMD mentioned by the WHO Collaborating Centre for Oral Cancer in 2020.

In summary, these observations elucidate the issue of inherited cancer syndromes with emphasis on FA but not Bloom syndrome, which could be classified as OPMDs. If Bloom syndrome is also classified as an OPMD, the epidemiologic, genetic, cytomorphometric, and clinicopathologic evidence of an inherited cancer syndrome like FA should be provided. It highlights that patients with FA should begin regular screening for head and neck cancer at the age of 10 years old or after hematopoietic stem cell transplantation. Reciprocally, young individuals who develop head and neck cancer should receive FA diagnostic tests. We are grateful to the editors who gave us an opportunity to provide this correspondence regarding inherited cancer syndromes, mainly Bloom syndrome and FA, classified as OPMDs.

Ethical approval

This work does not include human/animal subjects to acquire such approval, and then there is no relevant Judgement's reference number.

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Author contribution

W.L. and S.G.: screening and data extracting; W.L. and S.G.: writing – original draft; H.S. and X.S.: conceptualization and writing – review and editing.

Conflicts of interest disclosure

There are no conflicts of interest.

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Data availability statement

The data in this correspondence article is not sensitive in nature and is accessible in the public domain. The data is, therefore, available and not of a confidential nature.

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