## RESEARCH

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# Extensive and persistent tongue ulceration is an early character of dyskeratosis congenita



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### Abstract

**Background** Dyskeratosis congenita (DC) is a rare and fatal disease, presenting with a classic triad of skin pigmentation, nail dystrophy and oral leukoplakia. However, diagnosing DC is challenging based solely on the protean manifestations and multisystemic involvement. Therefore, it is urgent to identify an early feature facilitating initial suspicion of DC.

**Results** In this study, we enrolled a cohort of six male children diagnosed with DC, all of whom exhibited erosions or ulcers on the tongue, while five of them did not display the complete classic triad. Strikingly, oral erosions or ulcers have never been included in any existing clinical diagnostic criteria for DC. Through a retrospective analysis, we further demonstrated that extensive and persistent tongue ulceration emerges as an early and practicable clinical marker, provoking suspicion of DC even in the absence of the classic triad.

**Conclusions** Our findings challenge prevailing diagnostic criteria and advocates for an expanded consideration of tongue ulceration as a primary and indicative manifestation of DC, thereby affording a strategic advantage for early detection and intervention of this lethal disease.

Keywords Dyskeratosis congenita, Tongue ulceration, DKC1

### Introduction

Dyskeratosis congenita (DC) is fatal disease marked by multisystemic involvement with an incidence of 1/100, 000. DC presents with a triad of skin pigmentation, nail dystrophy and oral leukoplakia (OLK) [1]. The primary causes of mortality in DC are bone marrow failure (BMF), pulmonary disease and malignancies [2, 3]. In most cases, DC presented over the first two decades of

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In clinical practice, suspicion of DC guides the implementation of telomere measurement and targeted genetic testing, facilitating the definitive confirmation. The minimal clinical criteria for DC require the presence of at least two of the four major features, including abnormal skin pigmentation, nail dystrophy, OLK and BMF, as well as two or more somatic features [3, 7]. However, suspecting DC based solely on classic triad is challenging and often leads to delayed detection [7]. Some DC patients had none of the classic triad of DC [3, 8–11]. Thus, there



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is a pressing need of feasible manifestations for DC, which facilitates initial suspicion at early stages.

During our clinical practice, we noticed that DC patients at our institution had tongue ulcers or erosions, but not having the complete classic triad at first visits. Notably, oral ulcers or erosions have never been included in any existing clinical diagnostic criteria for DC [3, 7, 12, 13]. Based on these findings, we conducted a comprehensive investigation to determine whether oral ulceration could potentially serve as an early character for suspecting DC compared with the classic mucocutaneous triad.

#### **Patients and methods**

A literature search was conducted in PubMed, using the keywords 'Dyskeratosis congenita', to identify relevant English-language publications up until December 2022. The initial search yielded a total of 446 cases, which were subjected to rigorous evaluation to ensure medical accuracy. Two independent medical doctors meticulously reviewed the full texts of the retrieved articles, and a third doctor subsequently examined the analysis for consistency. Inclusion criteria for the analysis encompassed confirmed cases, while reports lacking unequivocal data on onset and diagnosis, as well as duplicate reports of the same case(s), were excluded.

Furthermore, six patients with DC were enrolled in West China Hospital of Stomatology, Sichuan University, and currently followed. Finally, a cohort of 452 DC patients was assembled, and a detailed analysis was conducted on the ages of diagnosing DC, the presence of the classic triad and genetic mutations. The presence of oral ulcerations was examined comprehensively, including an exploration of their ages and locations, while also establishing correlations with the classic triad.

Statistical analyses were carried out using R (version 4.0.3 software), and a significance level of p < 0.05 was defined to determine statistical significance.

#### Results

## Oral ulceration as an independent entity of DC: insights from two cases

Although oral ulceration has never been included in any existing clinical diagnostic criteria for DC, we are considering whether oral ulceration could potentially serve as an independent and early feature of DC, and whether patients with oral ulceration would progressively develop the classic triad. To address these questions, we focused on two representative cases within our cohort.

Case one involved a male patient of 1 year and 2 months old, who presented with 7-month ulceration on the dorsum and right side of the tongue. Oral examination revealed a sizable erosive surface on the dorsum of the tongue and both sides of the abdomen, with no other mucocutaneous abnormalities (Fig. 1A). Genetic testing indicated a mutation in the *DKC1* gene. qPCR analysis revealed the decreased telomere lengths of the patient, compared to the mother and a volunteer. Thus, a diagnosis of DC was made. This case suggests that oral ulceration may represent an independently early character of DC, separating from all the classic triad.

Case two involved a 4-year-old male patient in 2018 presented with whiteness and erosion of the lingual dorsum and bilateral lingual margins for one year. The original erosion lesion surface was partially covered with a



Fig. 1 Extensive oral ulceration in DC patients. (A) Images of tongue ulcers in a male DC patient at the age of 1 year and 2 months (Case 1). (B) Images of tongue erosions at the age of 4 years (left panel) and oral leukoplakia (OLK) at the age of 9 years (right panel) of a male DC patient (Case 2). (C) Images of tongue ulcers or erosions in other four cases of DC

pearlescent white pattern, and the erosion on both sides of the abdomen of tongue did not improve (Fig. 1B, left panel). There was hyperpigmentation on the posterior part of both buccal mucosae, and no other oral mucosa abnormalities were observed. Genetic testing revealed a pure-sibling mutation in *DKC1*, leading to a diagnosis of DC. During the recent follow-up in 2023, we found emergence of typical OLK in oral cavity (Fig. 1B, right panel). This case suggests a potential progressive development from oral ulceration to OLK in oral lesions. Finally, we presented typical oral ulceration images of other four DC patients in our cohort, indicating that extensive and persistent ulceration is an early character of DC (Fig. 1C).

## Oral ulceration as a feasible and early character for initial suspicion of DC

To better identify the initial manifestations of DC, we conducted a comprehensive review of the published literature and six DC patients from our cohort, with specific focus on oral ulceration.

In the cumulative group of 452 patients reported having DC (including six patients from our cohort), we identified a total of 34 DC patients with oral ulceration. Interestingly, unlike the scattered distribution of the classic triad with age, the character of ulceration was predominantly observed in children aged 0-10 years, and all reported cases of DC with oral ulceration were below the age of 30, which was earlier than the classic triad (Fig. 2A). Moreover, patients reported to have oral ulceration were significantly younger than those without oral ulceration, while patients reported to have OLK and skin pigmentation were older than those without OLK and skin pigmentation (Fig. 2B). Additionally, the presence or absence of nail dystrophy did not show a difference in age (Fig. 2B). All these facts support a notion that oral ulceration is an early character among the feasible manifestations of DC.

## Localization of oral ulceration and its association with *DKC1* mutations in DC

Next, we sought to investigate oral locations of ulceration. Results showed that among all the 34 cases, 47% patients exhibited ulceration localized on the tongue, and 12% cases with ulceration on both the tongue and buccal mucosa. Additionally, 3% cases reported ulceration occurrence on the buccal mucosa and oral cavity, respectively. Due to incomplete records in the literature, the ulceration sites of 35% patients remained unclear (Fig. 2C). The occurrence of DC is closely associated with various mutations in telomerase-related genes, like *DKC1*. Remarkably, it was observed that the incidence of *DKC1* mutations was significantly higher in DC patients with oral ulceration (56%) than those without oral ulceration (16%) (Fig. 2D). Due to the complexity of DC pathogenesis, diverse clinical presentations and variations in diagnostic criteria, there was a lack of genetic information in many cases. Notably, it revealed that the majority of oral ulceration occurred on the tongue, which was closely associated with *DKC1* mutations (Fig. 2E), suggesting a potential correlation between tongue ulceration and *DKC1* mutations in DC patients.

#### Discussion

The clinical spectrum of DC at presentation is broad, since the infiltration of different organs leads to the development of protean manifestations. Current literature identified abnormal skin pigmentation, nail dystrophy and OLK as the most common manifestations of DC. While the successive manifestations can occur over years, the clinical picture may be a slowly forming mosaic. In order to characterize the clinical manifestations of DC, we conducted a systematic review of published literature and included data from six patients in our cohort. Our findings indicate that extensive and persistent ulceration on the tongue even without the classic triad, represents a feasible character of DC, thereby facilitating initial suspicion and intervention strategies at early stages.

DC is characterized by the presence of the triad of skin pigmentation, nail dystrophy and OLK [3, 14], with clinical suspicion primarily based on recognizing these manifestations for nearly a century [14–17]. However, tongue ulceration may serve as an earlier and feasible clinical feature for DC suspicion. Previous reports have noted tongue ulceration in patients with DC [18, 19], and in 2019, we reported a DC case presenting with persistent tongue ulceration instead of typical OLK [20]. Despite updates in diagnostic criteria, oral ulceration remains unmentioned, even among the minor features of the disease. In light of these issues, our study aimed to identify ulceration as an ideal early manifestation and serves as a feasible character aiding in the early suspicion of DC. The diagnostic potential of tongue ulceration in DC is noteworthy for several reasons. Firstly, tongue ulceration emerges earlier compared with any classic triad for initial suspicion of DC. Secondly, tongue ulceration exhibits high specificity and can be distinguished from other mucosal manifestations, preventing misinterpretation as OLK, white keratotic lesions, white patches or lichenoid changes [21, 22]. Thirdly, given the wide range of clinical presentations in DC and the lack of definitive laboratory tests, particularly in undeveloped regions, the presence of pain associated with tongue ulceration captures the attention of both patients and physicians, facilitating early detection. Last but important, our findings demonstrate that tongue ulceration may serve as a specific indicator of the major subtype of DC with DKC1 mutation [<mark>3</mark>].



**Fig. 2** Tongue ulceration as an early character of DC. (**A**) Diagrams showing the distribution of ulceration and mucocutaneous triad related to patient ages. The dashed lines indicate the median ages. (**B**) Diagrams demonstrating that DC patients with oral ulceration exhibited significantly younger ages compared with those without oral ulceration, whereas the mucocutaneous triad exhibited an opposite trend. (**C**) Diagrams showing the distribution of ulceration sites in DC patients with oral ulceration, with the tongue being the most predominant location. (**D**) Diagrams showing the distribution of genetic mutations in DC patients, with a significantly higher proportion of *DKC1* mutations observed in DC patients with oral ulceration patients carried *DKC1* mutations

Mechanistically, DC carried mutations in genes such as *DKC1* leading to decreased telomerase activity and shortened telomeres, elucidating its genetic basis [7, 23–25] and linking it to telomere biology [26]. Notably, mutations in *DKC1* not only impair telomerase assembly and function but also compromise the pseudouridylation of ribosomal RNA. This dual impact underscores the severe phenotypes observed in X-linked DC cases. Tongue ulceration, as observed in our study, may result from heightened cellular turnover demands in rapidly regenerating mucosal tissues, exacerbated by impaired telomerase activity. Additionally, our studies highlight the role of other telomere-associated genes in modulating DC phenotypes. Variants in *TERT*, *PARN* and *NHP2*, are associated with severe disease subtypes, mirroring the effects of *DKC1* mutations [12, 27]. These genetic mutations further destabilize telomeres and compromise DNA repair mechanisms, contributing to persistent tissue damage such as mucosal ulceration.

#### Conclusions

In sum, our study highlights the clinical significance of tongue ulceration as an early manifestation of DC, suggesting that extensive and persistent tongue ulceration even in the absence of the classic triad or BMF, can raise suspicion of DC, enabling early detection and intervention.

#### Abbreviations

- DC Dyskeratosis congenita
- OLK Oral leukoplakia
- BMF Bone marrow failure
- HH Høyeraal-Hreidarsson

#### **Supplementary Information**

The online version contains supplementary material available at https://doi.or g/10.1186/s13023-025-03721-4.

Supplementary Material 1

#### Acknowledgements

Not applicable.

#### Author contributions

Xuefeng Zhang conceptualized and designed the study, collected data, performed analysis, drafted the manuscript, and performed the statistical analysis. Hongxia Dan, Yu Zhou and Wanxin Sun contributed to data acquisition and analysis. Wanchun Yang contributed to the concept and design of the study, supervised the work, and conducted the statistical analysis. Xin Zeng obtained funding for the study, and provided supervision. All authors have reviewed and approved the final manuscript.

#### Funding

This research was partially supported by the National Natural Science Foundation of China (Grant No. 82002877, U19A2005, 82270986).

#### Data availability

All data and analysis can be acquired from corresponding authors upon reasonable request.

#### Declarations

#### Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. All human work was approved by Institutional Review Board approval of the West China Hospital of Stomatology. Written informed consent was obtained from all included patients.

#### **Consent for publication**

Not applicable.

#### **Competing interests**

All authors declare no competing interests.

#### Received: 6 February 2024 / Accepted: 7 April 2025 Published online: 21 April 2025

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