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CASE REPORT

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Pachyonychia congenita with an unusual intraoral manifestation: case report

Abstract:

Pachyonychia congenita (PC) is a rare dermatosis impacting skin structures, appendages, and mucous membranes, primarily characterized by nail dystrophy, palmoplantar keratoderma, and plantar pain. Oral manifestation are particularly natal teeth and oral leukokeratosis and may be the earliest clinical signs. There is no specific treatment, the protocols are individualized and aim to alleviate symptoms. A 5-year-old boy came to the dentist's office complaining of a toothache. Intraoral examination revealed diffuse lesions scattered in the hard palate, marginal gingiva, alveolar mucosa, and tongue. Additionally, white plaques were observed on the lips at the boundary between the perilabial skin and the vermilion of the lip. Extraoral examination identified palmar lesions, skin lesions on the elbows and knees, as well as nail thickening and absence on the fingers and toes. Incisional biopsies of the lesion on the palate and on the belly of the tongue were performed and histopathological examination showed subepithelial clefts, dyskeratotic areas, hyperkeratosis, and acanthosis. Based on clinical and microscopic features, the diagnosis of PC (OMIM #167200) was established. Despite the typical skin alterations, the intraoral lesions shown in this case are atypical and uncommon. This case describes a young patient with typical skin and nail alterations and atypical and uncommon intraoral lesions related to PC and emphasizes the significant role of dentists in diagnosing syndromic conditions affecting the mouth.

Keywords: Pachyonychia congenita; Skin diseases, Genetic; Leukokeratoses, oral; Oral Medicine; Case report.

INTRODUTION

Pachyonychia Congenita (PC; OMIM #167200) is a rare genodermatosis inherited as an autosomal dominant trait and is caused by genetic mutations in genes related to collagen synthesis. Five genes (*KRT6A*, *KRT6B*, *KRT6C*, *KRT16*, and *KRT17*) may be related to the onset of the disease, but a mutation in just one of them is enough to manifest the condition[1,2]. PC is characterized by alterations in structures originating from the ectoderm, causing hypertrophic nail dystrophy, palmoplantar keratoderma, oral leukocytosis, pilosebaceous cysts, follicular keratosis, dental alterations, and pain when walking, directly impacting on the quality of life of those affected[3]. Diagnosis is based on clinical criteria and confirmed by identifying one of the pathological variants of the affected genes[3].

Statement of Clinical Significance
Pachyonychia congenita is a disease infrequently encountered in dental practices. Unusual oral lesions add to the complexity of diagnosing this condition. Individuals diagnosed with this disease should undergo oral examinations for screening and managing these lesions.

PC usually manifests in childhood, especially in school-age children, with nail changes being the first sign[1,4]. Previously, it was classified into two main subtypes based on the clinical presentation of the disease. PC-1 is called Jadassohn-Lewandowski syndrome and

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PC-2 is known as Jackson-Lawler syndrome[4,5]. The distinction between the two variants was made by clinical characteristics, with PC-1 often being associated with oral leukocytosis and mutations in the *KRT6a* and *KRT16*. The most common findings of PC-2 were theatocystomas or pilosebaceous cysts, capillary cysts in velus, capillary abnormalities, and natal teeth, and were related to mutations in the *KRT6B* and *KRT17*[1,3,5]. However, these differences are based on subtle phenotypic variations and do not apply to all affected individuals. For this reason, five clinical variants of PC are now recognized, based on the mutated keratin gene[1,4].

The prevalence of PC is a matter of controversy in the scientific literature since most of the information on the condition is found in case reports or small clinical case series. However, information from the International PC Research Registry (https://www.pachyonychia.org/) states that there are 1,700 affected individuals in more than 53 countries. Although the disease primarily manifests dermatological signs and symptoms that are more easily recognized, oral alterations have secondary importance and are underexplored in the literature. The aim of this paper is therefore to report a case of PC diagnosed after a visit to the dentist through the oral alterations observed in a pediatric patient.

CASE REPORT

A 5-year-old boy came to the dentist's office for an assessment of a molar complaining of pain. Intraoral examination revealed numerous reddish maculopapular lesions scattered over the hard palate.

In the gingival tissue, bleeding erythematous plaques were observed in the region of the free gingiva (Figure 1A); sometimes, the reddish lesions on the gingiva were replaced by plaques extending from the mesial interdental papilla to the distal interdental papilla, surrounding the tooth like a "collar", with the normal coloration of the oral mucosa (Figure 1C). On the belly of the tongue, there were well-defined whitish plaques with a smooth surface (Figure 1E). In addition, several teeth had cavities.

Examination of the peri labial mucosa and skin revealed small, slightly whitish keratotic nodules on the boundary between the vermilion of the lip and the skin.

Cutaneous examination revealed hypertrophic nail dystrophy in the fingers, with thick, yellowish, shortened nails, lateral angulation, and anonychia in some fingers and all toes (Figure 2A and D). In addition, skin lesions with a scaly appearance were observed in the areas where the skin folds, mainly on the knees fingers, and toes (Figure 2B and C). Areas of palmar keratoderma were also found. A summary of all the clinical changes found in the patient is available in Table 1.

Family history revealed similar lesions in the grandfather and two maternal uncles. It was noted

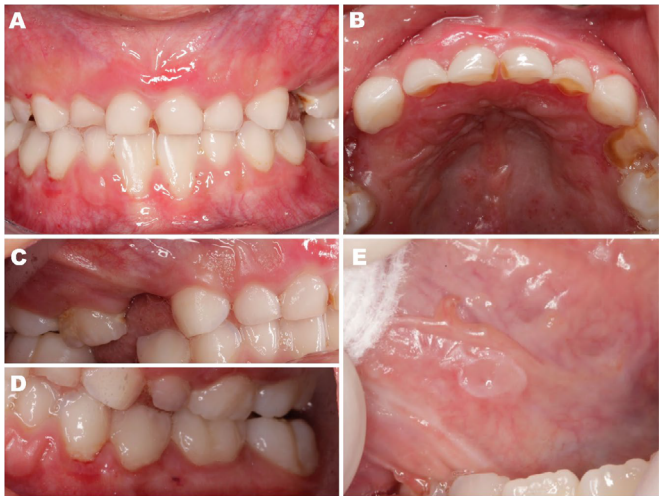

Figure 1. A: Diffuse gingival swelling situated at the gingival margin and gingival papilla surrounding the tooth. Erythematous and hemorrhagic spots on the gingival margin. B: Maculo-papular lesions on the hard palate and atrophic erythematous areas near the lingual gingival margin of the left premolar. C and D: Diffuse gingival swelling with normal mucosal color and erythematous, bleeding spots. E: A whitish lesion with an ulcerated surface on the ventral surface of the tongue.

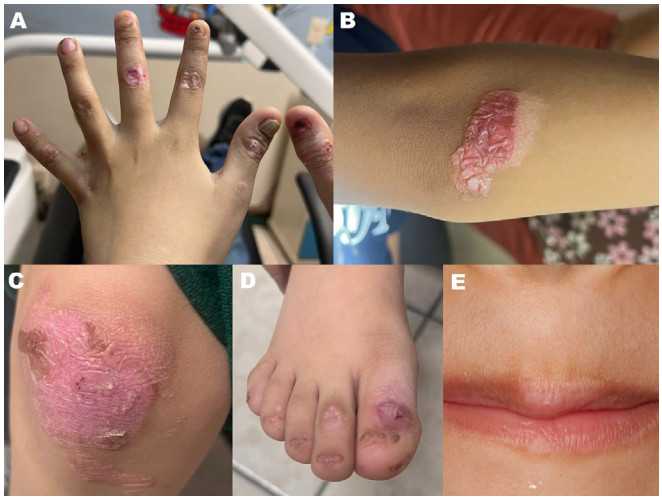

Figure 2. A: Nail thickening and absence of nails on the fingers. Hyperkeratotic lesions with a dry and scaly appearance in the areas of skin flexion. B and C: Hyperkeratotic lesions in the areas of skin flexion on the elbow and knee. D: Complete absence of toenails and lesions in the flexion areas of the toes. E: Whitish plaque at the boundary between the lip and the perilabial skin on the upper and lower lip.

Table 1. Summaries of the main clinical changes found in the patient with pachyonychia congenita.

	Tongue	Hard palate	Gingiva	Vermilion of the lip
Oral lesions	Well-defined whitish plaques	Reddish maculopapular lesions	Erythematous and whitish plaques Visible bleeding gums	Whitish keratotic nodules
	Nails	**Palms and soles**	**Fingers and toes**	**Elbows and knees**
Cutaneous lesions	Hypertrophic nail dystrophy Anonychia	Palmar and plantar keratoderma	Scaly appearance lesion	Scaly appearance lesion

that the child's lesions were a result of trauma. It was noted that the child's lesions were a result of trauma. Incisional biopsies of the tongue and of the palate lesion were performed and histopathological examination revealed hyperkeratosis and epithelial acanthosis. The keratinocytes exhibited a perinuclear halo, and areas of dyskeratosis were also observed. Furthermore, a subepithelial cleft was identified, leading to the complete detachment of the lining epithelium from the adjacent connective tissue, along with areas of ulceration. In the lamina propria, there was a chronic lymphoplasmocytic and subepithelial inflammatory infiltrate, along with numerous neoformed blood vessels (Figure 3).

Due to the hypothesis of herpetic gingivostomatitis, immunohistochemistry was carried out on the biopsied samples, which were negative for HSV-1 (Anti-Herpes Simplex Virus Type 1, Dako,1:7000, Carpinteria, CA). Considering the clinical findings, family medical history, and histopathological characteristics, a clinical diagnosis of PC was established. The patient was referred to a dermatologist for management of the skin lesions There is no specific treatment for the oral lesions of PC. Normally, protocols are individualized and aimed at relieving signs and symptoms. For the patient in question, the oral environment was adapted through cavity sealing, tooth extraction and mechanical biofilm control in addition to health education. The patient progresses with maintenance of the lesions.

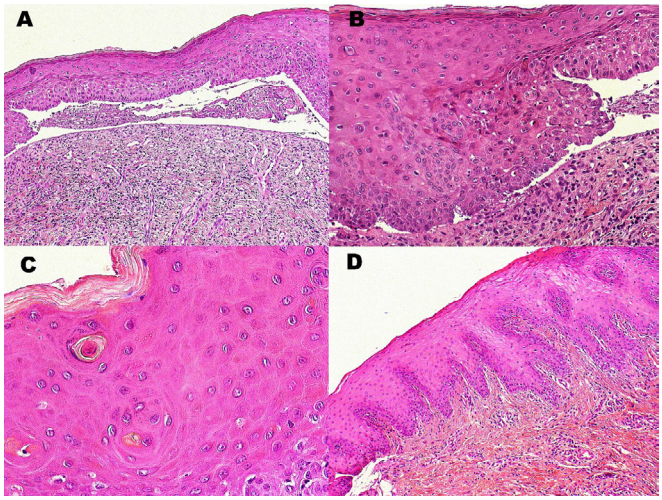

Figure 3. A: Fragment of palatine mucosa displaying keratinized squamous epithelium. A subepithelial cleft filled with fibrinous material and phagocytic cells is evident, along with dense connective tissue displaying a chronic inflammatory infiltrate (H&E; 100x). B: Epithelial cells exhibit perinuclear halo, dyskeratotic areas, and exocytosis (H&E; 200x). C: Fragment of squamous epithelium revealing dyskeratotic areas and premature keratinization (H&E; 400x). D: Tongue fragment showcasing squamous epithelium with hyperkeratosis and acanthosis (H&E; 100x).

DISCUSSION

PC is a rare genodermatosis caused by mutations in keratin synthesis genes, affecting skin and mucous membranes[2,6]. It is a missense-type genetic mutation that occurs when a single nucleotide substitution encodes a codon leading to the synthesis of an altered protein[4]. Although it was first described in the literature by Wilson, it was Jadassohn and Lewandowsky who coined the name of the disease[7]. It is an autosomal dominant condition of familial inheritance, as in this case, where there is probable involvement of other relatives such as the patient's grandfather and maternal uncles[8]. The diagnosis is usually made on the basis of clinical characteristics and confirmed by a genetic study[9].

Previously, two main types of the disease were recognized, but a more contemporary approach now identifies five types based on the mutated gene, dividing it into *PC-K6a*, *PC-K6b*, *PC-K6c*, *PC-K16*, and *PC-K17*[1]. The most common is PC type 1, associated with *KRT6A* mutations (*PC-K6a*), showing a range of symptoms such as plantar keratoderma, plantar pain, dystrophic fingernails, toenails, and prevalent oral leukokeratosis[1,6]. In this case, we observed lesions more indicative of *PC-K6a*, including nail dystrophy on the fingers and toes and oral leukokeratosis. Other symptoms across variants include cysts, follicular keratosis, and natal teeth, especially in *PC-K17*[4].

The most frequent clinical manifestation is hypertrophic nail dystrophy, which occurs in almost all cases and is evident at birth[1]. Affected individuals are usually diagnosed in early childhood, often within the first three years of life, with the appearance of lesions frequently associated with a history of trauma, as in this case[6]. Our patient presented with dystrophic changes in the fingernails and a complete absence of toenails. These nail abnormalities can affect at least two fingernails and all toenails, as observed in cases of *PC-K6a*, as described in the literature[1]. Another notable characteristic observed in this patient is the manifestation of hyperkeratotic lesions in regions of skin flexion, typically emerging following a history of trauma. Palmoplantar keratoderma is frequently observed, characterized by hyperkeratotic lesions with a coarse, dry texture, particularly on the soles of the feet, often causing discomfort during walking. Contrarily, this patient exhibited neither plantar lesions nor a history of pain in the affected area.

Oral alterations are common in PC, especially in the PC-K6a subtype[1,4,9]. The scientific literature indicates that oral leukokeratosis is the most frequent clinical manifestation in the mouth and mainly affecting the tongue and buccal mucosa[9]. It is characterized as a whitish, painless plaque with the tongue being the most common site[4]. A study involving 101 patients diagnosed with PC revealed that 70.3% of them exhibited oral leukokeratosis in the initial years of life[1,5]. However, other oral lesions were also found in our patient. Besides leukokeratosis on the tongue, lesions on the hard palate, gums, and lips were also observed. The lesions on the palate appeared clinically as reddish papules, and histological examination showed a subepithelial cleft and areas of deep chronic inflammation in the adjacent connective tissue. Leachman et al. indicated the occurrence of blisters preceding plantar lesions[10], the presence of vesiculobullous lesions on the oral mucosa in individuals with PC has not been previously documented. Furthermore, in patients with oral manifestations of the disease, previous histopathological analyses have not identified subepithelial clefts; instead, they have primarily reported hyperkeratosis and acanthosis[10].

A potential alternative diagnosis for this condition could be herpetic gingivostomatitis, a relatively common disease that often presents as the initial manifestation of herpes in children[11]. However, herpetic gingivostomatitis typically affects other oral areas and is accompanied by fever, malaise, and postration[11]; none of which were reported in this patient. Additionally, histopathological examination of herpes lesions typically reveals intraepithelial vesicles, acantholytic epithelial cells, and nuclear fragmentation with condensed and peripheral chromatin, which contrast with the findings in this case. Moreover, we performed anti-HSV1 immunohistochemistry on the paraffin-embedded tissue sample, which yielded negative results for both biopsied lesions. However, a condition like herpetic gingivostomatitis, being a viral disease, typically resolves on its own within 10-14 days[11] — a resolution that did not occur in this case. On the contrary, the lesions changed in appearance and worsened.

Regarding the gingival lesions, we noted an enlargement in tissue volume in the free gingiva, forming a collar around the entire tooth, along by punctate hemorrhagic areas. Although the gingiva exhibited swelling and bleeding at specific points, the possibility of gingivitis was ruled out. Despite the presence of biofilm and suboptimal oral hygiene habits, the clinical presentation in this case differs from typical gingivitis, which generally resolves within a few days with the establishment of good oral hygiene practices, an outcome not witnessed in this particular case. On the lips, at the boundary between the vermilion and the skin, nodules of normal mucosal color were noted which were not biopsied. These findings are not common in patients with PC of any subtype and, as far as we know, have never been described in individuals with PC.

Dyskeratosis congenita (DC) is a multisystemic inherited disease with a predilection for males[12]. Affected individuals exhibit nail changes, oral leukoplakia, and reticular hyperpigmentation[12,13]. Unlike DC, the leukokeratosis seen in individuals with PC does not show areas of epithelial dysplasia and does not progress to malignant transformation over time[12]. Additionally, DC presents with extracutaneous signs and symptoms, such as bone marrow failure leading to opportunistic infections, thrombocytopenia, bone abnormalities, cardiovascular diseases, gastrointestinal disorders, malignant neoplasms, and other conditions, typically indicating a poor prognosis[9,12]. In this case, the diagnosis was established based on clinical manifestations[9]; however, our patient lacked reticular hyperpigmentation or a history of other systemic diseases. Moreover, the histopathological analysis of the oral lesions did not reveal epithelial dysplasia. Considering these factors collectively, the diagnosis of PC was favored.

Regarding dental alterations, Duverger et al. (2018) demonstrated that individuals with PC type K6a, K6b, and K6c are more prone to developing dental caries.

The study suggests that ameloblasts can synthesize defective keratin, incorporating it into the organic enamel matrix, which results in enamel that is structurally less resistant to bacterial acttivity[14]. Indeed, the patient in this study presented with carious lesions in multiple teeth, including toothache, which prompted the visit to the dentist. However, despite these findings, the patient also displayed poor oral hygiene habits and dental biofilm, factors that independently increase the prevalence of caries in individuals in this age group.

The oral and skin alterations observed in our patient are typical in individuals with PC. However, the oral mucosal lesions documented in this patient, to our knowledge, have not been previously reported in the literature. While oral leukokeratosis is common in individuals with PC, especially in areas subjected to attrition and trauma, vesicularbullous lesions on the hard palate, hemorrhagic lesions on the gingiva and alveolar mucosa, and the pattern of gingival edema with areas of erythema or normal mucosal color, as well as lip lesions, have not been documented in the literature. Whether this represents a novel clinical manifestation of the disease or another overlapping condition remains unclear. It is known that most studies describing PC's clinical characteristics are predominantly conducted by physicians less accustomed to examining the oral cavity. What distinguishes this report is that the diagnosis was made by a team of dentists specializing in oral medicine and oral pathology, bringing expertise in craniofacial manifestations of syndromic conditions. The emphasizing the important role of dentist in diagnosing systemic diseases and syndromes affect the head and neck region.

PC has no cure or specific treatment. Some studies[4,8] recommend interventions aimed at managing the signs and symptoms of the disease to enhance the quality of life for affected individuals. Conservative treatments include lifestyle adjustments, the use of mobility aids such as canes, crutches, or wheelchairs, analgesics to control plantar pain and retinoids to soften skin lesions. Surgical approaches may also be employed when necessary, involving the removal of calluses, blisters, excesses tissue, and cystic lesions[4,8]. The oral lesions described in this case are, to the best of our knowledge, the first to be documented and reported in the literature. It is still too early to definitively conclude whether these alterations in oral tissues represent an expansion of the disease phenotype. Therefore, further studies are needed to assess the occurrence of oral lesions consistent with those reported in this case.

CONCLUSION

Pachyonychia congenita can be diagnosed through clinical findings, with genotyping used to determine the subtype and predict signs and symptoms. This report emphasizes the role of the dental surgeon in diagnosing syndromic diseases with oral manifestation based on clinical findings. Further studies conducted by oral medicine professionals are essential to better characterize the oral manifestations of PC.

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AUTHOR'S CONTRIBUTIONS

EGSL: conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft. AERS: data curation, formal analysis, investigation. JLBC: data curation, formal analysis, investigation. HKFB: formal analysis, investigation, methodology, resources. RMP: conceptualization validation, visualization, writing – original draft, writing – review & editing. HMJ: conceptualization validation, visualization, writing – original draft, writing – review & editing.

CONFLICT OF INTEREST STATEMENT

Funding: This word did not receive any specific grant from funding agencies.

Competing interests: The authors state that they have no potential conflict of interest that could bias the results obtained in the current study.

Ethics approval: This study was conducted in accordance with current ethical standards and consent was obtained from the patient.

REFERENCES

1. Shah S, Boen M, Kenner-Bell B, Schwartz M, Rademaker A, Paller AS. Pachyonychia congenita in pediatric patients natural history, features, and impact. JAMA Dermatology. 2014;150(2):146-53. https://doi.org/10.1001/jamadermatol.2013.6448
2. Zieman AG, Coulombe PA. Pathophysiology of pachyonychia congenita-associated palmoplantar keratoderma: new insight into skin epithelial homeostasis and avenues for treatment. Br J Dermatol. 2020;182(3):564-73. https://doi.org/10.1111/bjd.18033

3. Smith FJD, Hansen CD, Hull PR, Kaspar RL, Irwin McLean WH, O'Toole E, et al. Pachyonychia congenita. In: Gene Reviews. Seattle: University of Washington; 1993. PMID: 20301457.
4. Mccarthy RL, Brito M, O'Toole E. Pachyonychia congenita: clinical features and future treatments. Keio J Med. 2023. https://doi.org/10.2302/kjm.2023-0012-IR
5. Eliason MJ, Leachman SA, Feng BJ, Schwartz ME, Hansen CD. A review of the clinical phenotype of 254 patients with genetically confirmed pachyonychia congenita. J Am Acad Dermatol. 2012;67(4):680-6. https://doi.org/10.1016/j.jaad.2011.12.009
6. Rathore PK, Khullar V, Das A. Pachyonychia congenita type 1: case report and review of the literature. Indian J Dermatol. 2016;61(2):196-9. https://doi.org/10.4103/0019-5154.177761
7. Agarwal P, Chhaperwal M, Singh A, Verma A, Nijhawan M, Singh K, et al. Pachyonychia congenita: a rare genodermatosis. Indian Dermatol Online J. 2013;4(3):225-7. https://doi.org/10.4103/2229-5178.115527
8. Daroach M, Dogra S, Bhattacharjee R, Afra T, Smith F, Mahajan R. Pachyonychia congenita responding favorably to a combination of surgical and medical therapies. Dermatol Ther. 2019;32(5):e13045. https://doi.org/10.1111/dth.13045
9. Cantile T, Coppola N, Caponio VCA, Russo D, Bucci P, Spagnuolo G, et al. Oral mucosa and nails in genodermatoses: a diagnostic challenge. J Clin Med. 2021;10(22):5404. https://doi.org/10.3390/jcm10225404
10. Leachman SA, Kaspar RL, Fleckman P, Florell SR, Smith FJD, Irwin McLean WH, et al. Clinical and pathological features of pachyonychia congenita. J Investig Dermatol Symp Proc. 2005;10(1):3-17. https://doi.org/10.1111/j.1087-0024.2005.10202.x
11. Heliotis I, Whatling R, Desai S, Visavadia M. Primary herpetic gingivostomatitis in children. BMJ. 2021;375:e065540. https://doi.org/10.1136/bmj-2021-065540
12. AlSabbagh MM. Dyskeratosis congenita: a literature review. J Dtsch Dermatol Ges. 2020;18(9):943-67. https://doi.org/10.1111/ddg.14268
13. Savage SA. Dyskeratosis congenita and telomere biology disorders. Hematology Am Soc Hematol Educ Program. 2022;2022(1):637-48. https://doi.org/10.1182/hematology.2022000394
14. Duverger O, Carlson JC, Karacz CM, Schwartz ME, Cross MA, Marazita ML, et al. Genetic variants in pachyonychia congenita-associated keratins increase susceptibility to tooth decay. PLoS Genet. 2018;14(1):e1007168. https://doi.org/10.1371/journal.pgen.1007168