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Atypical oral features of patient with neurofibromatosis type 1: case report

Características orais atípicas de paciente com neurofibromatose tipo 1: relato de caso

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ABSTRACT

The purpose of this article is to assist dental clinicians to identify neurofibromatosis type 1 and its variants. We present a rare case of a 68-year-old man affected since his childhood by the presence of generalized nodules throughout the body, causing aesthetic deformations. Interestingly, the impact in the oral cavity was not significant, presenting nodes only in the gingiva, an unusual area of manifestation. Panoramic radiograph showed a discrete enlargement of the mandibular canal. After 1 year of follow-up, the patient died due to cardiovascular complications caused by the syndrome.

Key words: mouth abnormalities; neurofibroma; nerve tissue.

RESUMO

O objetivo deste artigo é auxiliar os dentistas clínicos a identificar a neurofibromatose tipo 1 e suas variantes. Apresentamos um raro caso de um homem de 68 anos de idade, acometido desde a infância pela presença de nódulos generalizados em todo o corpo, causando deformações estéticas. Curiosamente, o impacto na cavidade oral não foi significativo, apresentando nódulos apenas na gengiva, uma área de manifestação incomum. A radiografia panorâmica mostrou um discreto aumento do canal mandibular. Após um ano de seguimento, o paciente faleceu devido a complicações cardiovasculares causadas pela síndrome.

Unitermos: *anormalidades da boca; neurofibroma; tecido nervoso.*

RESUMEN

El propósito de este artículo es ayudar a los dentistas clínicos a identificar la neurofibromatosis tipo 1 y sus variantes. Presentamos un caso raro de un hombre de 68 años, afectado desde la infancia por la presencia de nódulos generalizados en todo el cuerpo, provocando deformaciones estéticas. Curiosamente, el impacto en la cavidad oral no fue significativo, con nódulos solo en la encía, un área de manifestación raro. La radiografía panorámica mostró un ligero agrandamiento del canal mandibular. Tras un año de seguimiento, el paciente falleció por complicaciones cardiovasculares provocadas por el síndrome.

Palabras clave: *anomalias de la boca; neurofibroma; tejido nervioso.*

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INTRODUCTION

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen syndrome, is an autosomal dominant disorder caused by germline mutations in the NF1 tumor suppressor gene. NF1 can affect bones, nervous system, soft tissues, and skin[1, 2]. There are two other forms of NF, including NF type 2, which is a rare centered form that affects the central nervous system, and schwannomatosis[2-4].

NF1 is one of the most common genetic disorders in humans, with a prevalence of 1 in 3,000 births[5]. The disease is manifested by the presence of cutaneous nodules that may be isolated or diffuse throughout the body, causing aesthetic and facial deformity, skeletal and behavioral abnormalities, and pigmented lesions (cafe-au-lait spots)[1, 2]. Additionally, 3% to 15% of these cutaneous nodules may undergo malignant transformation[4].

Oral manifestations of NF1 are defined by the presence of soft tissue tumors, bone defects, periodontal and dental abnormalities, as well as altered salivary flow[6]. Several authors report that approximately 4%-7% of the cases of NF1 can appear associated with some oral manifestations, while others suggest that these manifestations are present in up to 72% of the cases[7]. Most of the soft tissue lesions appeared on the tongue. Lesions in other oral sites, such as gingiva, are more rarely seen (~ 5% of cases)[8, 9]. Besides, bone defects are the result of increased osteoclast activity or the presence of intraosseous tumors, which are commonly seen in the posterior region of the mandible[6, 10]. We report a case of a patient with NF1, presenting distinct oral manifestations of the disease. With this article, we aim to assist dentists to perform the correct diagnosis and appropriate management of NF1.

CASE REPORT

A 68-year-old male of short stature, presenting scoliosis, multiple nodules throughout the body since childhood, and absence of cafe-au-lait spots in the skin (**Figure 1**). One of those nodules was removed from the eyelid and diagnosed as neurofibroma. The patient was diagnosed with neurofibromatosis von Recklinghausen's type 1 arises *de novo*, since no one in his family had a similar condition. Previous medical history revealed that he was also hypertensive.

In terms of oral health, his main complaint was the difficulty to eat because of "loose teeth". Intraoral examination revealed poor oral hygiene, dental caries, tooth mobility, resorption of alveolar ridges, and multiple pedicular nodules located in the anterior region of the superior alveolar ridge. Those nodules were painless, rosy, soft, and measured approximately 4 mm in diameter (**Figure 2**). No change in lingual papillae was observed. Panoramic radiograph shows a discrete enlargement of the mandibular canal and preservation of other bone structures, such as mandibular ramus and coronoid notch (**Figure 3**).

As a result of poor oral conditions, the remaining teeth and multiple intraoral nodules were removed. The patient underwent prosthetic rehabilitation, although its use was interrupted by the recurrence of a few nodular lesions in the alveolar ridge. We referred the patient for plastic surgery to remove a few large dermal nodules that were causing discomfort due to the increased size. After 1 year of periodic follow-up, the patient died due to cardiovascular complications.

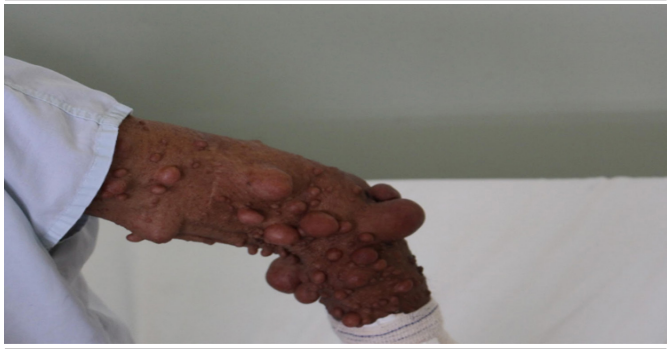

FIGURE 1 – *Presence of multiple diffuse nodules throughout the body*

FIGURE 2 – *Intraoral aspect*

A) presence of few gingival nodules in anterior maxilla region; B) normal pattern of the tongue without changes in the papillary level.

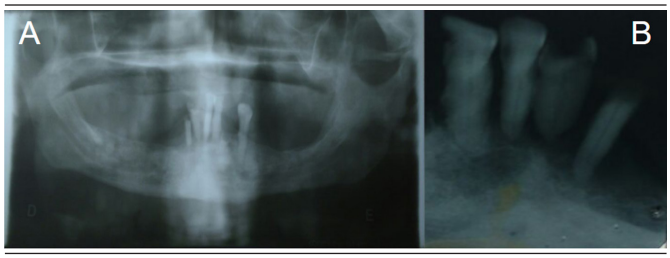

FIGURE 3 – *Radiograph exam*

A) panoramic radiograph revealed discrete enlargement of the mandibular canal and normal appearance of the mandible's border and coronoid notch; B) periapical radiograph. Alveolar bone loss caused by periodontal disease. No increase in cortical bone density was observed.

DISCUSSION

NF1 affects multiple organ systems and has a highly variable clinical manifestation[2]. Patients with NF1 may present oral alterations in various tissues, including bones, mucosa, and salivary glands[6, 10]. The average age of NF1 patients is 27.5 years, and women are more commonly affected than men[3]. A high number of neurofibromas is associated with the neurofibromatosis von Recklinghausen's type 1, especially in the head and neck due to the rich innervation in these areas[1, 3, 10]. Although it may appear anywhere on the skin, they are less common in the face[1, 4]. In contrast to that data, our patient presented several generalized neurofibromas all over his face, causing aesthetic deformity and even compromising his vision. Moreover, these tumors are more frequent in superficial soft tissue than a deeper layer[3, 10].

Individuals with NF1 have a high risk of skeletal abnormalities, with scoliosis being the most prevalent skeletal pathology[11]. Also, neurological complications are observed in 55% of the cases. As a result, the most common neurophysiological disturbances involve cognitive defects and learning difficulties[12]. Our patient had localized skeletal deformities, while neurological changes were not observed.

According to the literature, oral manifestations can be found in almost 72% of the cases[4, 13]. Due to the rarity and variability of NF, it is very difficult for researchers to identify a satisfactory number of patients with specific clinical characteristics or *germline* mutations to participate in intervention studies[5]. Sarmento *et al*. (2017)[14] presented a rare case of NF1, in which the patient not only showed neurofibromas, but also giant cell lesions and florid cemento-osseous dysplasia.

In cases of intraoral manifestation of neurofibroma, branches of the fifth and seventh cranial nerves are potentially involved, while the ninth cranial nerve is rarely affected[15]. Occasionally, the proximity of neurofibromas with cranial nerves may result in impairment of the motor function of the facial and hypoglossal nerves and thus alter the sensitivity of the trigeminal nerve[7, 16]. Common sites for oral neurofibromas include the tongue, oral mucosa, alveolar crest, labial mucosa, palate, nasopharynx, paranasal sinuses, larynx, the floor of the mouth, and salivary glands[9, 14, 17], while the gingiva represents an uncommon area for the appearance of these lesions[9]. Among main clinical manifestations of the disease are high prevalence of hyposalivation[18] and increased projection of fungiform papillae, which occurs in 50% of the cases and it is the most frequent finding[4]. Our patient did not show any alterations in fungiform papillae, with tongue maintaining its normal anatomy and only alterations in gingiva were visible.

Radiographically, remarkable findings of NF include lengthening, narrowing and rarefaction of the coronoid process, deepening of the sigmoid notch, an increase of the mandibular canal and the mental foramen[19], as well as the shortening of the mandibular ramus[10, 20]. Besides, there is a connection between mandibular asymmetry and neurofibromatosis[7, 21], and a correlation with macrodontia and excess dental caries[22]. In our case, none of these radiological alterations were observed. Literature findings of the last five years corresponding to these characteristics can be seen in **Table**.

When the neurofibromas grow or cause pain, there must be a suspect of malignant transformation and a biopsy must be performed[3]. The emergence of complications due to malignant transformations occurs in 6%-29% of the cases, generally with poor prognosis and survival rate of five years[20]. In another study, the rate of malignant transformation was approximately from 5% to 16%[16]. Manuscripts related to NF1 from the last five years (Table) mentioned a single case involving a patient with oral breast cancer metastasis, showing an association between NF1 and breast cancer[23]. In general, oral alterations in patients with NF1 require ongoing follow-up, and frequently, surgical excision is mandatory[7].

TABLE – Summary of clinical and radiographic data from the last five years

Authors	Type of study	Oral clinical manifestations	Oral radiographic findings
Sarmento *et al*. (2017)[14]	Clinical case	Giant cell lesion and florid cemento-osseous dysplasia	Not reported
Friedrich *et al*. (2017)[21]	Research	Not applicable	Asymmetry in the facial skeleton, no changes in the sella turcica
Mahmud *et al*. (2016)[15]	Clinical case	Neurofibroma in tongue	Not reported
Shekar *et al*. (2015)[9]	Clinical case	Neurofibroma gingival	Not reported
Cunha *et al*. (2015)[18]	Research	High prevalence of hyposalivation	Not reported
Visnapuu *et al*. (2012)[19]	Research	Not applicable	Increased diameter of the mandibular canal
Kobayashi *et al*. (2012)[22]	Research	Not applicable	Macrodontia and excess of dental caries

CONCLUSION

It is important to recognize oral alterations in patients with NF1. Neurofibromas may be the first manifestation of von Recklinghausen's syndrome or the representation of the development of other lesions. It is known that nodules are recurrent, so it is crucial to keep patients under observation, carrying out a long-term follow-up in order to track new changes and treat them accordingly.

REFERENCES

1. Ghalayani P, Saberi Z, Sardari F. Neurofibromatosis type I (von Recklinghausen's disease): A family case report and literature review. Dent Res J. (Isfahan). 2012; 9(4): 483-8.

2. Gutmann DH, Ferner RE, Listernick RH, Korf BR, Wolters PL, Johnson KJ. Neurofibromatosis type 1. Nat Rev Dis Prim. 2017; 3.

3. Kumar CA, Reddy RCJ, Gupta S, Laller S. Oral hamartomas with von Recklinghausen disease. Ann Saudi Med. 2011; 31(4): 428-30.

4. Shetty B, Umesh Y, Kranti K, Seshan H. Periodontal manifestations of von Recklinghausen neuro fibromatosis. J Indian Soc Periodontol. 2013; 17(2): 253.

5. Seidlin M, Holzman R, Knight P, et al. Characterization and utilization of an international neurofibromatosis web-based, patient-entered registry: an observational study. PLoS One 2017; 12(6).

6. Cherifi H, Fournier B, Berdal A, McAlpin B, Sitbon IY, Gogly B. Oral Manifestations of Neurofibromatosis Type 1. J Cosmet Dermatological Sci Appl. 2019; 9(1): 41-55.

7. Cunha KSG, Barboza EP, Dias EP, Oliveira FM. Neurofibromatosis type I with periodontal manifestation. A case report and literature review. Br Dent J. 2004; 196(8): 457-60.

8. Shapiro SD, Abramovitch K, van Dis ML, et al. Neurofibromatosis: oral and radiographic manifestations. Oral Surg Oral Med Oral Pathol. 1984; 58(4): 493-8.

9. Shekar V, Rangdhol V, Baliah WJ, Thirunavukarasu S. An unusual oral manifestation of type 1 neurofibromatosis: a case report and review of literature. J Nat Sci Biol Med. 2015; 6(1): 261.

10. Bharath TS, Krishna YR, Nalabolu GR, Pasupuleti S, Surapaneni S, Ganta SB. Neurofibroma of the palate. Case Rep Dent. 2014; 2014: 1-4.

11. Krishnamoorthy B, Singh P, Suma GN, Sharma ML, Dhillon M. Notching in the posterior border of the ramus of mandible in a patient with neurofibromatosis type I – a case report. J Clin Diagnostic Res. 2013; 7(10): 2390-1.

12. Arun KP, Thomas Joseph P, Jaishankar HP, Abhinethra MS. Von Recklinghausens disease: a series of four cases with variable expression. J Maxillofac Oral Surg. 2015; 14(Suppl 1): 161-7.

13. Sharma A, Sengupta P, Das AK. Isolated plexiform neurofibroma of the tongue. J Lab Physicians. 2013; 5(2): 127-9.

14. Sarmento DJS, de Carvalho SHG, de Araújo Filho JCWP, Carvalho MV, da Silveira EJD. Florid cemento-osseous dysplasia and peripheral giant cell granuloma in a patient with neurofibromatosis 1. An Bras Dermatol. 2017; 92(2): 249-52.

15. Mahmud SA, Shah N, Chattaraj M, Gayen S. Solitary encapsulated neurofibroma not associated with neurofibromatosis-1 affecting tongue in a 73-year-old female. Case Rep Dent. 2016; 2016.

16. Narang BR, Palaskar SJ, Bartake AR, Pawar RB, Rongte S. Intraosseous neurofibroma of the mandible: a case report and review of literature. J Clin Diagnostic Res. 2017; 11(2): ZD06.

17. Bekisz O, Darimont F, Rompen EH. Diffuse but unilateral gingival enlargement associated with von Recklinghausen neurofibromatosis: a case report. J Clin Periodontol. 2000; 27(5): 361-5.

18. Cunha KS, Rozza-De-Menezes RE, Luna EB, et al. High prevalence of hyposalivation in individuals with neurofibromatosis 1: a case-control study. Orphanet J Rare Dis. 2015; 10(1).

19. Visnapuu V, Peltonen S, Tammisalo T, Peltonen J, Happonen RP. Radiographic findings in the jaws of patients with neurofibromatosis 1. J Oral Maxillofac Surg. 2012; 70(6): 1351-7.

20. Rath R, Kaur S, Baig SA, Pati P, Sahoo S. Multifocal head and neck neurofibromas with osseous abnormalities and muscular hypoplasia in a child with neurofibromatosis: type I. Case Rep Radiol. 2016; 2016: 1-7.

21. Friedrich RE, Lehmann JM, Rother J, et al. A lateral cephalometry study of patients with neurofibromatosis type 1. J Craniomaxillofac Surg. 2017; 45(6): 809-20.

22. Kobayashi R, Matsune K, Ohashi H. Fused teeth, macrodontia and increased caries are characteristic features of neurofibromatosis type 1 patients with NF1 gene microdeletion. J Pediatr Genet. 2012; 1(1): 25-31.

23. Nilesh K, Naniwadekar RG, Vande AV. Large solitary neurofibroma of face in a paediatric patient. J Clin Diagnostic Res. 2017; 11(6): ZD04.

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