Exuberant manifestation of neurofibromatosis type 1 affecting 3 generations: delayed diagnosis and the importance of the multidisciplinary approach

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Neurofibromatosis type 1 (NF1) is an autosomal dominant inherited disorder caused by mutations of chromosome 17. The NF1 clinical diagnosis is based on pre-established criteria, including the presence of cutaneous neurofibromas, café au lait spots, and iris (Lisch) nodules. Early detection and a multidisciplinary approach are essential for the prevention of complications, including problems of function, aesthetics, and self-esteem, as well as the occurrence of malignant transformation. This study reports a case of an exuberant NF1 manifestation diagnosed by a dental surgeon, whose investigation of a family led to the diagnosis of NF1, with different expressivities, in 3 generations. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:e108−e112)

Neurofibromatosis type 1 (NF1), or Von Recklinghausen's disease, is an autosomal dominant inherited disorder caused by mutations or deletions of the neurofibromin gene on chromosome 17 q11.2,[1,2] regardless of sex, ethnicity, or place of birth.[3,4] This multifactorial disease is basically composed of skin alterations, genetic abnormalities, and neurologic problems,[2,5,6] with an incidence of 1:2500/3000.[2,7]

NF1 is primarily characterized by café au lait spots, multiple cutaneous neurofibromas, Lisch nodules (iris hamartomas), central nervous system tumors, macrocephaly, mental disability, and bone problems[8] and has a significant impact on quality of life.[9] Oral neurofibromas are noted in 3.4% to 92% of adults and 40% of children with NF1.[10] Cutaneous neurofibromas represent the most remarkable alterations.

It is of primary importance for dental surgeons and dermatologists to be knowledgeable about the signs and symptoms of NF1 to achieve an early diagnosis, thus optimizing early intervention for aesthetic issues and preventing functional and emotional complications. This study reports a case with an exuberant manifestation of NF1, and an investigation of the patient's family led to the diagnosis of NF1 in her offspring.

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Received for publication Feb 12, 2019; accepted for publication Mar 2, 2019.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2019.03.003

CASE REPORTS

A 59-year-old edentulous white woman was referred to the UniCesumar Dental School for general dental rehabilitation. On general examination, multiple sessile cutaneous papules and softened pinkish nodules all over the face, trunk region, and arms were observed (Figures 1A−1D). Also, some discrete café au lait spots were detected. Further evaluation revealed Lisch nodules (Figure 1E). The patient also had scoliosis and apparent orthopedic alterations in the arms.

In the intraoral examination, a solitary well-defined painless swelling, measuring approximately 1 cm and firm in consistency, was observed in the palate posterior region. Radiographic screening was normal. On the basis of these characteristics, a presumptive diagnosis of traumatic fibrous hyperplasia or a minor salivary gland tumor was hypothesized. However, because of the patient's general condition, oral neurofibroma was also considered. Microscopic analysis of the excisional biopsy specimen of the oral lesion showed mature fibrous connective tissue with discrete nervous bundles and possible spindle cells with elongated nuclei, as well as numerous mast cells. Immunohistochemical study revealed positivity for the S-100 protein, confirming the diagnosis of neurofibroma (Figure 2).

The patient was informed about the pathology and the genetic implications. Surprisingly, she had never been diagnosed with this condition before. When asked about family history, she reported that her mother also had similar lesions; therefore, the mother was also asked to present for examination.

The 86-year-old woman had an exuberant manifestation of sessile and pedunculated nodules on the face, neck, scalp, and upper and lower limbs; the nodules were soft and asymptomatic (Figure 3). The highest concentration of nodules occurred on the trunk, with lesions of different sizes (Figure 4). Lisch nodules and a solitary nodule approximately 1 cm in size and located in the left

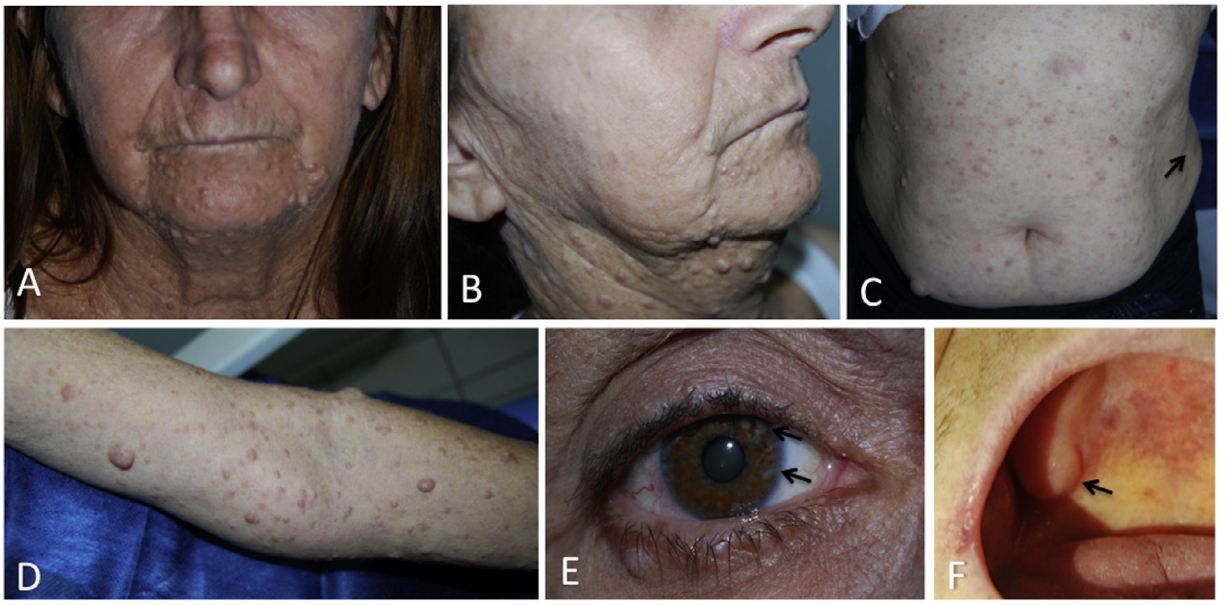

Fig. 1. Mother, 59 years old. Sessile papules and nodules on the face **(A)**, neck **(B)**, trunk **(C)** and arm **(D)**. The arrow indicates the presence of a café au lait spot on her trunk. Lisch nodules **(E)** and a neurofibroma on the hard palate **(F)** were also observed.

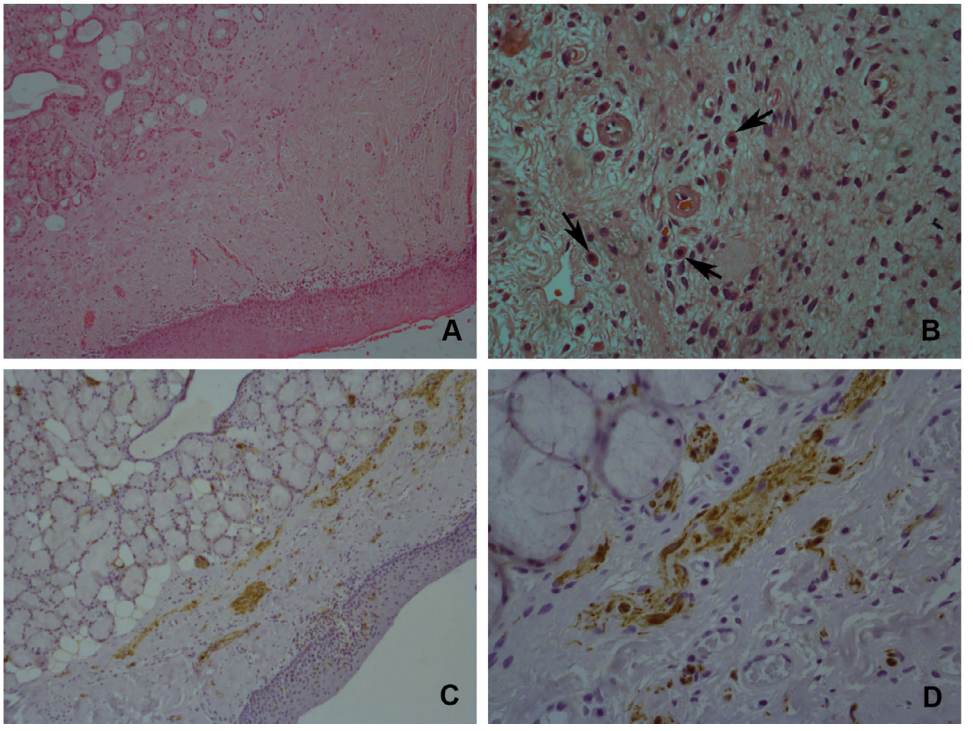

Fig. 2. Histopathologic features of neurofibroma. Dense fibrous connective tissue **(A)** hematoxylin and eosin; magnification × 10) with discrete spindle cells with elongated nuclei and numerous mast cells *(arrow)* **(B)** hematoxylin and eosin; magnification × 40). Diffuse immunostaining for S-100 neural molecule **(C)** magnification × 10), sometimes with fusiform arrangement, characteristic of neural formations **(D)** magnification × 40).

jugal mucosa were also detected (Figure 5). An evident abnormal posture indicated severe scoliosis. The patient reported having anxiety problems and dissatisfaction with her physical appearance, besides difficulty with maintaining body hygiene. The mother was also not aware of her condition.

Continuing the investigation in the patient's family, we requested the presence of the patient's daughter for

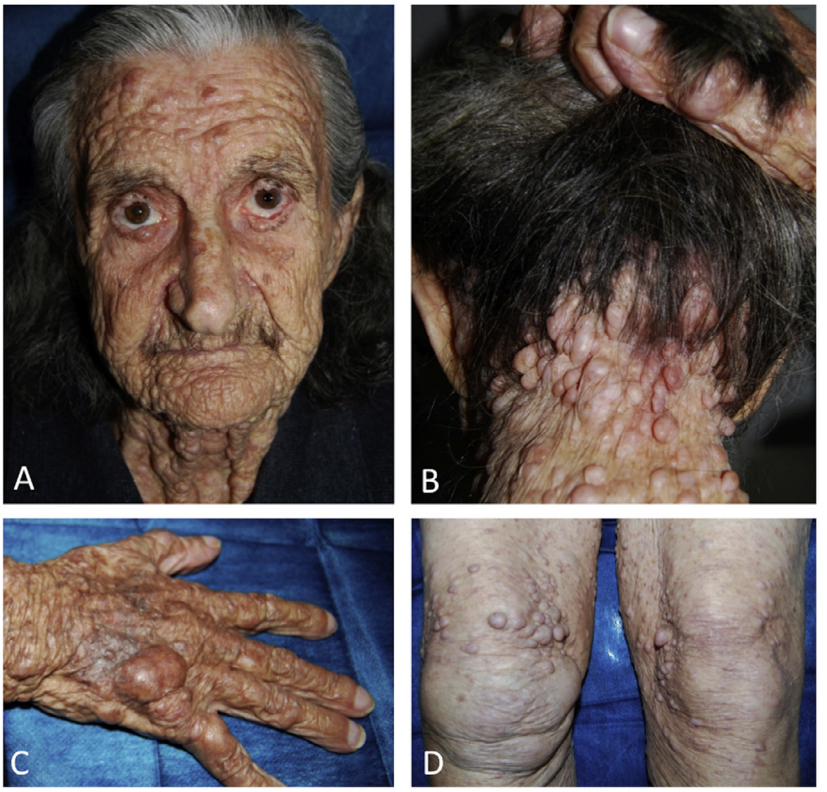

Fig. 3. Grandmother, 86 years old. Multiple nodules on the face **(A)**, neck and scalp **(B)** A huge nodule on the right hand **(C)**, and some concentrated nodules on the legs **(D)**.

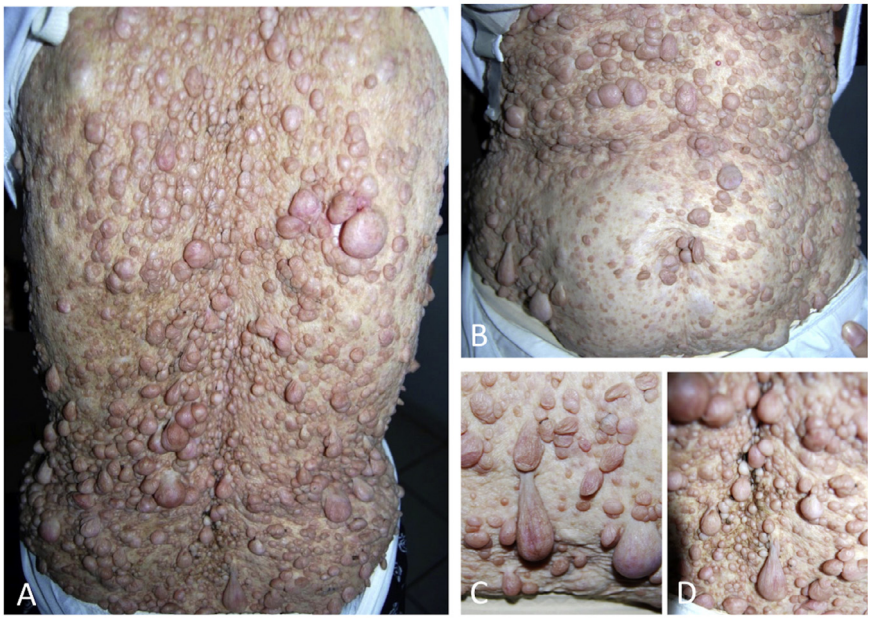

Fig. 4. Grandmother, 86 years old. Multiple sessile and pedunculated nodules on the posterior **(A)** and anterior **(B)** trunk. The magnified images show different sizes and shapes of nodules **(C** and **D)**, whose conglomeration impaired the hygiene.

evaluation. The 20-year-old woman had mental disability, scoliosis, and multiple café au lait spots (with sizes ranging from 4 to 6 cm) throughout the body (Figure 6). Oral lesions were not observed.

On the basis of the clinical and family data, we had a strong suspicion of NF1. The 3 patients were referred for dermatologic, orthopedic, neurologic, ophthalmic, and genetic evaluations. Family history involving other

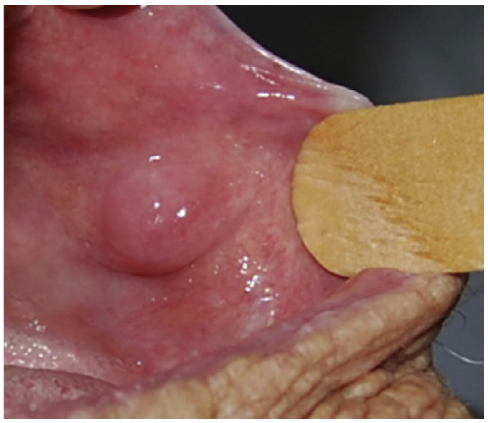

Fig. 5. Grandmother, 86 years old. Asymptomatic pinkish sessile nodule, approximately 1 cm in size, on the left jugal mucosa, suggesting an oral neurofibroma.

members were denied. We decided to monitor the grandmother's oral lesion because she refused to undergo biopsy, claiming to be debilitated. Dental care was offered to all 3 patients, and long-term periodic follow-ups were scheduled.

DISCUSSION

The clinical diagnosis of NF1 is based on criteria established by the National Institutes of Health in 1987,[11] reaffirmed in 1997.[8] It must include 2 or more of the following characteristics: 6 or more café au lait spots; 2 or more neurofibromas of any type or 1 plexiform neurofibroma; ephelides in the axillary or inguinal regions; optic glioma; 2 or more Lisch nodules; typical bone damage—sphenoid bone dysplasia or thinning of the cortex of long bones; a first-degree relative with NF1, diagnosed according to the aforementioned criteria. These changes may be associated with neurologic and cognitive problems, scoliosis and other bone abnormalities, and malignant tumors.[12]

Considering these criteria, the present cases were clinically classified as NF1 because of the 3 patients, 2 showed cutaneous neurofibromas (grandmother and mother), 2 showed Lisch nodules (grandmother and mother), 1 showed oral plexiform neurofibroma (mother), and 2 showed café au lait spots (mother and granddaughter). Possibly, the grandmother's oral nodule was a neurofibroma, but the diagnosis could not be confirmed microscopically. Certain characteristics, such as the granddaughter's mental disability and the scoliosis in the 3 patients, reinforced the diagnosis. Scoliosis is the most frequent bone alteration in NF1, present in about 25% of cases, ranging from mild to severe lesions. Its etiology has not yet been fully elucidated, but mesodermal dysplasia has been associated.[13]

NF1 is inherited from parents in about 50% of cases. Patients with no family history suggest a high incidence of new mutations.[14] The disease usually occurs in 1 or 2 generations; but, in some families, it occurs in 4 to 6 generations.[8,15] The term *expressivity* refers to the variability of clinical or physical signs associated with a specific gene. NF1 is one of the genetic diseases that best exemplifies this phenomenon because a wide clinical variability exists, even within a family. Moreover, a severely affected patient may produce offspring with a milder clinical condition, and vice versa.[15] The reported cases illustrate 3 affected generations, with different expressivities. The grandmother probably manifested the first mutation, considering that other family members were not reported to have the disease.

The patients were referred for medical evaluation for further investigation, especially of the cutaneous neurofibromas, because malignant transformation

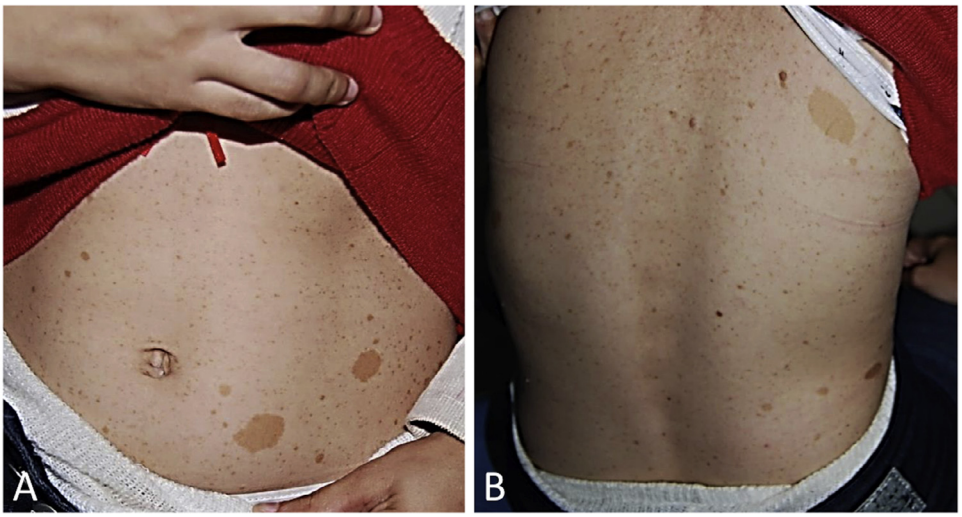

Fig. 6. Granddaughter, 20 years old. Multiple café au lait spots in the posterior **(A)** and anterior **(B)** trunk. As the patient had a mental disability, she was wearing diapers.

of into neurogenic sarcomas was possible. In addition, internal neurofibromas, which can be potentially malignant, may affect vital organs,[16] resulting in severe morbidity and even death.[7,9] Moreover, various neurologic pathologies, such as hamartoma of the iris, neurinoma of the acoustic nerve, tumors of the central nervous system (gliomas, glioblastomas), macrocephaly, and mental retardation,[17] may occur, justifying the importance of a multidisciplinary approach. The third-generation family member had severe mental disability, and for this reason, genetic counseling could not be performed. It is, however, recommended because of the probability of vertical transmission.

NF1 has an important impact on patients' quality of life,[7] with cosmetic deformities being reported as the main problem.[7,9] Cutaneous neurofibromas affect patients' aesthetics and self-esteem.[4] Moreover, an unpredictable progression of the disease may cause anxiety in patients and family members.[9] The disease is a true assault on self-image, affecting physical appearance, learning process, job performance, and, consequently, economic status. For this reason, psychological monitoring is also essential.

It is of primary importance for dental surgeons, dermatologists, orthopedists, neurologists, ophthalmologists, psychologists, and geneticists to be knowledgeable about the signs and symptoms of NF1 to achieve an early diagnosis and to avoid complications. This report emphasizes the role of a thorough approach to all patients with NF1 and demonstrates the importance of the role of the dental surgeon in this process, as demonstrated in the present cases, where the diagnosis of the disease was established in a dental appointment.

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