

PLEXIFORM NEUROFIBROMA CLINICALLY CONSISTENT WITH NEUROFIBROMATOSIS TYPE I: A CASE REPORT

Neurofibroma clinicamente compatível com neurofibromatose tipo I: relato de caso

Joseph E. Chasteen¹

Dolphine Oda²

Abstract

Neurofibromatosis type I is a common autosomal dominant disease affecting from 1:2500 to 1:3000 newborn with 50% mutation and almost 100% penetrance. While nine types have been described, type I accounts for more than 90% of cases and is well delineated. We present a case of a 43-year old white male who presented to the Emergency Clinic at the University of Washington in Seattle, Washington, with "dull pain in the right lower jaw" of three months' duration. He had multiple carious teeth and multiple soft tissue swellings in the mouth, head and neck area and other parts of his body. This case report describes the clinical characteristics of NF1, including the oral manifestations and an a clinically applicable differential diagnosis of this disease.

Keywords: Plexiform neurofibroma, neurofibromatosis, von Recklinghausen's neurofibromatosis, chromosome

Resumo

A neurofibromatose tipo I é uma doença autossômica dominante que afeta de 1:2500 a 1:3000 recém-nascidos, com 50% de mutação e 100% de penetrância. Enquanto nove tipos tenham sido descritos, o tipo I responde por mais de 90% dos casos e é bem delineado. Apresenta-se um caso de paciente de 43 anos, masculino, branco, que procurou a Clínica de Emergência da Universidade de Washington, em Seattle, WA, queixando-se de "dor surda na maxila, lado direito" com três meses de duração. Apresentava múltiplos dentes cariados e aumentos de volume múltiplos nos tecidos bucais, cabeça e pescoço, bem como em outras partes do corpo. Este relato de caso descreve as características clínicas da neurofibromatose tipo I (NF1), incluindo as manifestações bucais e o diagnóstico diferencial clinicamente aplicável desta doença.

Palavras-chave: Neurofibroma plexiforme; Neurofibromatose; neurofibromatose de von Recklinghausen; Cromossoma 17q11.2.

¹ DDS, MA. Associate Professor, Department of Oral Medicine, School of Dentistry, University of Washington in Seattle, Washington.

² BDS, MSc. Professor, Division of Oral Pathology, Department of Oral Surgery, School of Dentistry, University of Washington in Seattle, Washington

Address:

Joseph E. Chasteen, DDS, MA

Director, Office of Educational & Information Technology Box 356370 1959 N.E. Pacific Avenue

Seattle, WA 98195-6370 e-mail:chasteen@u.washington.edu

Introduction

Neurofibromatosis type I (NF1) was first described by Frederick von Recklinghausen in 1882 and for that reason has also been known as von Recklinghausen's neurofibromatosis (1-5). It is one of the most common autosomal dominant diseases with equal gender manifestation. It affects 1:2,500 to 1:3,000 newborn with 50% mutation and almost 100% penetrance (1-3). The genetic abnormality of NF1 is mapped to chromosome 17q11.2(6-8).

The protein is known as neurofibromin and is 220-kDa in size (8). It is known to control cellular growth and differentiation and functions as a tumor suppressor gene (6,7). Nine types have been described (1); types I and II are the most common and are well delineated while the other types are rare and not well studied (1-3). Type I accounts for more than 90% of cases(1-5), followed by type II, which is also known as acoustic type, where bilateral acoustic neuromas are described leading to hearing loss starting as early as the teenage years (9). Type II is much less common and affects 1 in 40,000 individuals.

The genetic mutation of NF1 is mapped to chromosome 22 (9). The diagnosis of NF1 is made on the basis of a group of clinical manifestations following the established NIH criteria proposed in 1988 (11). It includes cutaneous neurofibromas, café-au-lait spots (five or more of 1.5 cm size and larger in adults and 0.5 cm or larger in puberty and under), axillary freckling (Crowe's sign) and Lisch nodules among many others. A group of investigators from Montreal, Canada (3), reviewed 279 pediatric cases of NF1 and found that the average age of manifestation was 3.4 years (range 0-15.3).

Over 50% of patients manifest the disease at the first year of life (1). Café-au-lait spots are the first manifestation of the disease and was found in 99% of the patients in the pediatric group from Montreal Canada (3). The cutaneous nodules represent benign neurofibromas and are of variable sizes ranging from mms to

pendulous masses several pounds in weight. They are present in about 40% of patients at the early age(1,3).

Neurofibromas are not just confined to the skin and mucous membranes; they can also be present with visceral organs such as the heart and lungs, brain and the gastrointestinal tract. The cutaneous neurofibromas can occur as early as at birth and increase in number with time and can number from a few to in the thousands. These patients may also develop skeletal abnormalities including scoliosis in about 10-15% of patients, pseudarthrosis of the tibia, and partial overgrowth of an extremity (12).

It may affect the central nervous system such as in mental retardation described in 8% of the patients(1-3). It may also affect the cardiovascular system such as pulmonic valvular stenosis, the endocrine system such as sexual precocity (2). Eyes are also involved such as neurofibromas of the eyelids, Lisch nodules of the iris affecting up to 82% and optic gliomas affecting up to 14% of the patients (3). (Figure 1)



Figure 1.- Neurofibromas of the eyelids.

Oral soft tissue manifestations of neurofibromatosis can occur in 8-66% of cases (5,10), mostly in the soft tissue part of the mouth. Some involve the jaws, especially the mandible in 58% of patients (5,10). In the mouth, the most common lesion is neurofibroma, which occurs mostly in the soft tissue, especially in the tongue. It may also affect the jaw bones such as the mandibular foramen and inferior alveolar canal, as is the case in our patient (1,5,10). Other lesions include hyperplasia of the fungiform papillae and displacement of teeth as well as blocking tooth eruption.

Histologically, the neurofibromas can be the conventional, more common type of haphazardly arranged neural tissue in a relatively demarcated nodule or can be the

plexiform type where nerve tissue is arranged in lobules. The latter histology is pathognomonic of neurofibromatosis(1-2). In the head and neck area plexiform neurofibroma can be associated with the trigeminal nerve branches.

Treatment in Neurofibromatosis patients is primarily for esthetic and functional reasons. Scalpel surgery, laser or dermabrasion treatments have been used for the removal of skin neurofibromas. Malignant transformation has been described in about 4-7% of patients(1-5) most of which are peripheral nerve type malignancies which tend to be aggressive. Other malignancies have been described including leukemia, rhabdomyosarcoma, Wilm's tumor, Pheochromocytoma among others (1-3).

Case report

A 43-year old white male presented to the Emergency Clinic of the School of Dentistry at the University of Washington in Seattle, Washington with "dull pain in the right lower jaw" of three months' duration. The patient had attempted previously to save teeth #s 30 & 31 that had extensive damage due to caries. Both teeth were tender to percussion with failing restorations. In addition to the carious teeth, this patient had multiple soft tissue swellings in the mouth, head and neck area, as well as other parts of his body. (Figure 2)

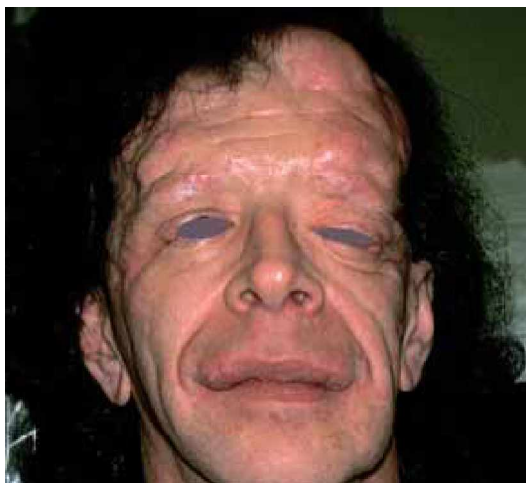


Figure 2. - Multiple soft tissue swellings on the patient's face.

The patient is an adopted child and therefore was not aware of a family history of parents or siblings with multiple nodules. His past medical history is otherwise unremarkable.

Clinical and Radiographic Findings

The clinical examination revealed numerous nodules on the head and neck region, including the mouth. The nodules were smooth-surfaced and were of variable shape and size. (Figure

3) In the mouth the nodules involved the buccal mucosa, lips and palate. (Figure 4)



Figure 3. - Numerous nodules on the head and neck region.



Figure 4. - Multiple nodules on the lips and buccal mucosa. Also notice the gingival hyperplasia at the edentulous left maxilla.

Hyperplasia of the gingiva at the left maxilla was associated with irregular-looking alveolar bone (Figure 5). Teeth numbers 1, 17 and 32 were impacted. Teeth numbers 17 and 32 demonstrated dentigerous cysts with irregular bone overlying the cysts. The

alveolar nerve canal was slightly widened at the right side . Most of the remaining teeth

A periapical radiograph of the mandibular right molar teeth revealed

demonstrated secondary caries.

extensive fractures and caries in teeth numbers 30 and 31. (Figure 6)

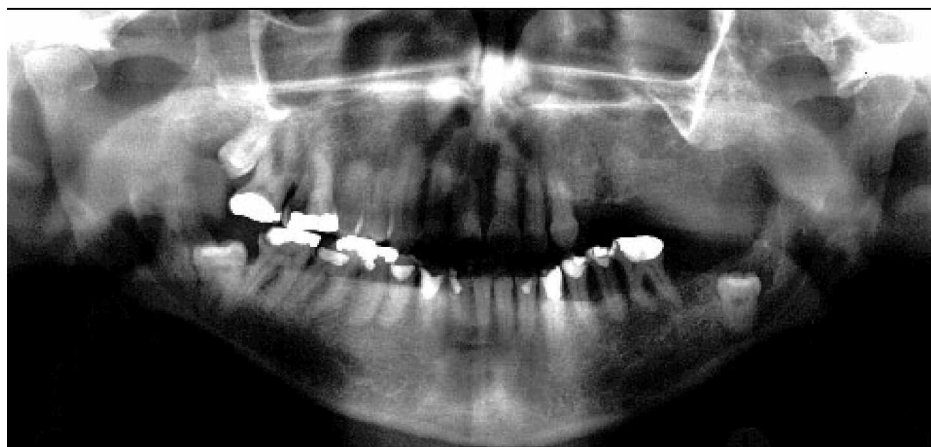


Figure 5. - Panoramic view at first presentation demonstrating many failing restorations, three impacted teeth, irregular bone structures at the left maxilla and mild expansion of the inferior alveolar canal at the right side of the mandible.



Figure 6 - Periapical radiograph of the mandibular right molar area.

Incisional and Excisional Biopsy
 An incisional biopsy of a buccal nodule revealed a piece of oral mucosa covered with stratified squamous epithelium and supported by connective tissue which was almost completely occupied by a lesion of neural origin. The latter was made up of lobules of myxoid neural tissue, in some areas, with central nerve bundles. These lobules are surrounded by a connective tissue capsule (Figure 7). The neural bundles were made up of spindle-shaped cells with

wavy nuclei suspended on a delicate background of collagen fibers. Immunohistochemistry markers with S-100 protein were positive for nerve fibers (Figure 8).

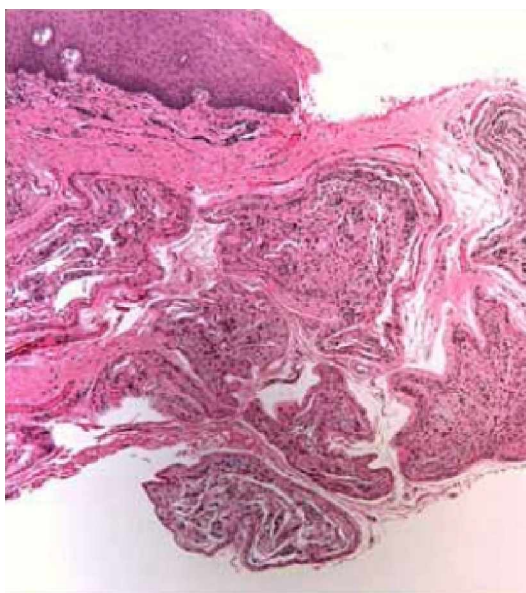


Figure 7. - Low power (x100) histology shows multiple lobules of well-demarcated nerve tissue separated by denser connective tissue.

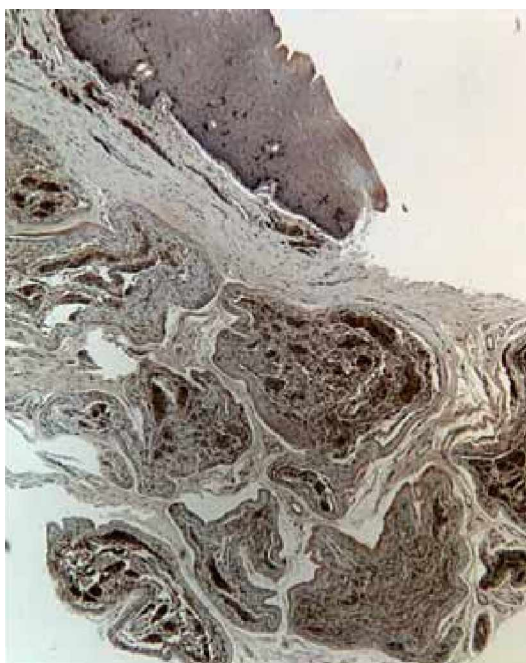


Figure 8 - Low power (x100) immunohistochemistry using antibody to S-100 protein. The nerve lobules are positive with central areas of more concentrated staining consistent with a central nerve bundle.

Treatment of the Chief Complaint

Tooth #30 was extracted. The patient chose to retain tooth #31 through endodontic treatment and a crown restoration.

Discussion

The diagnosis and treatment of the patient's chief complaint was routine and unremarkable. However, the diagnosis of plexiform neurofibroma, clinically consistent with neurofibromatosis Type I was more complex.

The oral presentation of multiple soft tissue nodules, although pathognomonic for NF1, it demands an appropriate differential diagnosis which should include: tuberous sclerosis complex (TSC); multiple hamartoma syndrome; and multiple endocrine neoplasia (MEN) 2b syndrome.

Tuberous sclerosis complex (TSC) Tuberous sclerosis Complex is a common neurocutaneous syndrome with multiple skin nodules. It is autosomal dominant with 70% spontaneous mutation. TSC is characterized by seizures, multiple cutaneous hamartomatous growths and central nervous system disorders such as mental retardation (13). The multiple cutaneous growths can involve organs other than the skin. Two types of this syndrome are described and the genes have been mapped to chromosome 9 for TSC1 and chromosome 16 for TSC2 (1,13). The clinical presentation of this syndrome ranges from mild and undiagnosed to severe. The prevalence varies from 1:23,000 to 1:170,000; autopsy studies indicate its incidence rate in the general population to be as high as 2.5% (1,13).

Among the clinical manifestations are skin lesions such as angiofibromas, mostly occurring around the nasolabial fold. They are smooth-surfaced red nodules; they can also involve the nails. Hypopigmentation (Ashleaf spots) also occurs and sometimes requires special light for identification. The latter is the first symptom to appear-sometimes at birth-and is the most common presentation. Other significant lesions include subependymal nodules of the brain; 90% of patients with this condition develop seizures and 60% are

mentally deficient. Cardiac rhabdomyomas are described in 30% of patients. Renal, ocular and skeletal abnormalities are also described. The histology and the clinical presentation of this case are not supportive of TSC (1,13).

Multiple Hamartoma Syndrome

This is a rare disease complex involving the skin, breast, gastrointestinal tract and thyroid. It is autosomal dominant and the gene has been mapped to chromosome 10q23. Skin lesions are papillomatous and smooth surfaced nodules and occur in about 99% of patients with this condition. They occur mostly on the face, particularly around the eyelids, nose, mouth and ears. They may also affect the arms and hands. The nodules are mostly trichilemmomas, of hair follicle origin. Breast diseases include fibrocystic disease and some malignant neoplasms. Thyroid lesions include goiter, follicular adenocarcinoma, and polyps; these are typically benign in behavior. The histology and the clinical presentation of this case are not supportive of TSC (14,15).

Multiple Endocrine Neoplasia (MEN) 2b syndrome

These are rare disease groups affecting the endocrine system. Three types have been described. Some are inherited as autosomal dominant while others develop as a result of mutation. MEN syndrome type 2b is the most significant type to dental practitioners. The gene for this type has been mapped to chromosome 20p12.2. Lesions appear as early as infancy, causing problems with feeding and normal thriving (16). During the first decade, multiple small mucosal nodules occur in the oral cavity on the anterior tongue, lower lip, and bilateral corner of mouth. These nodules are highly characteristic of the disease. They may also occur on the eyelids and conjunctiva, and represent multiple neuromas which are histologically made up of hyperplastic peripheral nerve fibers. Multiple melanotic skin lesions have been described in these patients. Patients have marfanoid features, a

thick lower lip, and an everted upper eyelid. They also develop pheochromocytoma, profuse sweating, diarrhea, and severe hypertension. In addition, they often develop medullary carcinoma of the thyroid at around 18-25 years of age, but this aggressive neoplasm has been described in patients as young as 23 months. MEN 2b patients demonstrate high levels of catecholamines and calcitonin if pheochromocytoma and medullary carcinoma are present. Preventive removal of the thyroid gland is recommended (16). The clinical presentation and histology of this case are not supportive of MEN 2b syndrome.

Conclusion

The general dentist may be the first person to make the primary diagnosis of neurofibromatosis, as was the case with this patient. Therefore, it is important to know of this disease and its characteristic clinical manifestations. These patients should be referred to physicians for further clinical and genetic workup.

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