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Case Report

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Diagnosis and treatment of an unusual case with multiple intra-oral growths of neural tissue origin

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Abstract

A 27-year-old female patient in this case study had several growths along the lateral border and ventral surface of tongue. The patient also had multiple skin swellening and café au lait pigmentation. Histopathological examination revealed hyperplastic stratified squamous epithelium and proliferating fibrous tissue with chronic inflammatory infiltrates in the tongue growths. Immunohistochemical analysis using Sox 10, Ki67 and S100 markers confirmed high cellular proliferation and neural differentiation in the lesions, respectively. The findings led to the diagnosis of neurofibromatosis type I (NF1). This case highlights the importance of considering NF1 in the differential diagnosis of oral neurofibromas, especially in patients with multiple skin manifestations, and emphasizes the need for regular follow-ups to monitor disease progression and manage potential complications.

Keywords: Café au Lait pigmentation, Nodules, Schwannoma, Ventral surface of tongue, Von Recklinghausen's disease.

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INTRODUCTION

Neurofibromas are the most common peripheral nerve sheath tumor. There are three main types of neurofibromas: localized, diffuse, and plexiform. the plexiform type is pathognomonic for neurofibromatosis type 1 (NF1) and carries an increased risk of malignant transformation. Neurofibromatosis type I, also known as von Recklinghausen's disease, is a autosomal dominant disorder primarily affecting the skin and nervous system. It is characterized by the development of neurofibromas, benign tumors originating from Schwann cells, which can arise throughout the body, including the tongue and skin. NF1 is caused by mutations in the NF1 gene, leading to dysregulation of cell growth and proliferation [1]. NF-I of the tongue associated with skin manifestations represents a rare and distinct subtype of NF1. In this variant, patients exhibit neurofibromas specifically affecting the tongue, along with characteristic skin lesions. These skin manifestations commonly include café-au-lait spots, axillary freckling, and cutaneous neurofibromas. The presence of multiple neurofibromas on the tongue can result in a range of symptoms, such as speech difficulties, swallowing problems, and cosmetic concerns, significantly impacting the quality of life for affected individuals [2]. The diagnosis of NF1 with tongue involvement and skin manifestations requires a comprehensive clinical examination, including both dermatological and neurological assessments, in addition to genetic testing for NF1 mutations [3]. Management of NF1 typically necessitates a multidisciplinary approach to address the various symptoms and potential complications that may arise [4]. While NF1 is extensively documented in the medical literature, studies specifically focusing on NF1 of the tongue associated with skin manifestations are limited due to its rarity. Consequently, there is a need for further research to better comprehend the underlying pathogenesis and develop targeted therapeutic strategies for this unique subtype [5]. This case report presents a 27-year-old female patient with complaints of multiple growths in the tongue and anterior aspect of the lingual mucosa of the lower jaw. The short review to provide an overview of NF1 of the tongue associated with skin manifestations, shedding light on its distinct clinical presentation and challenges in diagnosis and management. Understanding the intricacies of this rare condition can facilitate better patient care and contribute to the advancement of medical knowledge in the field of neurofibromatosis.

CASE REPORT

Clinical presentation

This case report presents a 27-year-old female patient with complaints of multiple growths in the tongue and anterior aspect of the lingual mucosa of the lower jaw. The patient had a history of skin lesions that began seven years ago, characterized by multiple swellings and café au lait pigmentation. After the extraction of lower anterior teeth, the patient expressed the desire for a prosthesis. The patient presented with multiple painless, raised growths in the left border and the ventral surface of the tongue, and on anterior lingual mucosa of the lower jaw. The lesions were of varying sizes and exhibited a granular and verrucous appearance [Figures 1a-b]. Additionally, multiple swellings were noted on the skin, scattered across the body especially on the upper and lower limbs, along with the presence of café au lait pigmentation [Figures 2a-d]. The growths were surgically removed, and sutures were used to close the wounds (Figure 1c). For histological and immunohistochemical analysis, the removed tissues were submerged in 10% formalin solution.

Figure 1: Illustrates (a-b) multiple painless, raised growths on the ventral surface of the tongue and on anterior lingual mucosa of the lower jaw, and (c) wound site after surgical removal of growths. [Note: arrow indicates nodular growths intraorally (white arrow) and extraorally (black arrow).]

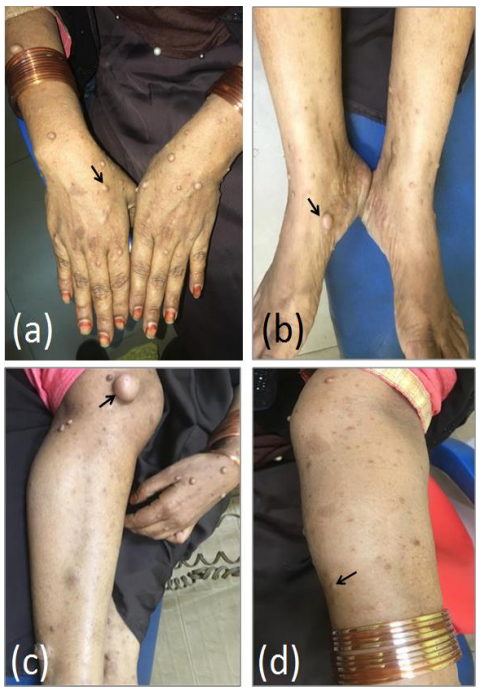

Figure 2: Shows (a-d) multiple swellings on the skin, scattered especially on the upper and lower limbs, along with the presence of café au lait pigmentation. [Note: arrow indicates nodular growths.]

Histopathological Examination

A biopsy of the tongue growth was performed to investigate the nature of the lesions. Microscopic examination revealed hyperplastic and hyperkeratotic stratified squamous epithelium. The underlying connective tissue showed proliferating fibrous tissue with varying degrees of vascularity. Chronic inflammatory infiltrates were also observed in the stroma [Figure 3a].

Immunohistochemical Findings

Immunohistochemistry (IHC) was conducted using Sox 10, Ki67 and S100 markers to assess the proliferative and neural characteristics of the lesions, respectively. Ki67 is a marker for cellular proliferation, while S100 is a marker for neural tissues. Ki67 IHC staining demonstrated a high proliferation index in the epithelial cells of the tongue growths, indicating increased cellular division and potential for rapid growth [Figure 3b]. S100 IHC staining revealed positive staining in some cells within the lesions, suggestive of neural differentiation [Figure 3c].Sox10 showed positiveexpression forthe nerve tissue and not for the schwann cell [Figure 3d]. These findings suggested a possible neurogenic origin for the growths.

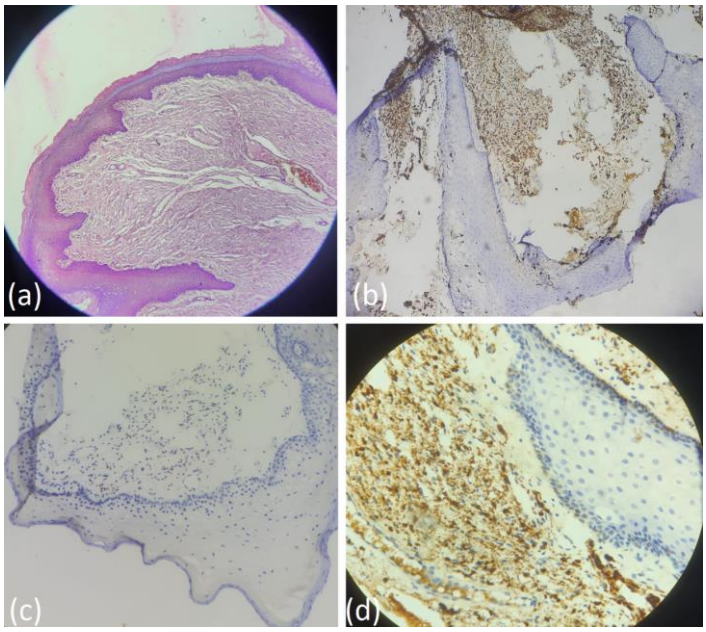

Figure 3: Shows (a) hyperplastic and hyperkeratotic stratified squamous epithelium, and collection of nerve cells and varying degrees of vascularity in the proliferating fibrous connective tissue with H&E staining; and (b) Immunohistochemical staining with Ki67 demonstrates a high proliferation index in the epithelial cells; (c) staining with S100 demonstrating positive staining in some cells within the lesions, suggestive of neural differentiation; and (d) staining with Sox 10 demonstrating positive expression in nerve cells.

Diagnosis

Based on the clinical, histopathological, and immunohistochemical findings, the patient was diagnosed with neurofibromatosis type 1 (NF1).

DISCUSSION

Neurofibromatosis type 1 (NF1) is a rare genetic disorder characterized by benign tumors called neurofibromas, affecting approximately one in 3000 people [6,7]. These tumors can range from small nodules to large masses and have a firm consistency, growing slowly over time. Though typically painless, they can cause discomfort due to nerve compression. Histological analysis of neurofibromas typically reveals fusiform cells with wavy nuclei, surrounded by delicate collagen bundles in a variable myxoid stroma. The presence of mastocytes is common and assists in diagnosis [8].

Neurofibromas can occur independently, but they are often associated with NF1, with oral lesions being the most common. NF1 and NF type 2 are distinct conditions linked to dominant autosomal genetic alterations. NF1 results from a mutation in the NF1 gene on chromosome 17, impacting the function of the tumor suppressor protein neurofibromin [9,10]. The diagnosis of NF1 is based on specific clinical criteria, first described by Von Recklinghausen in 1882, including

café-au-lait skin macules, skin neurofibromas, freckles in the groin and armpit areas, pigmented iris hamartomas (Lisch nodules), and optic glioma, among other manifestations involving bone and nerve tissues. The patient in this case report met two or more of these criteria, confirming the diagnosis of NF type 1 [1,7]. Oral neurofibromas are rare but represent the most common neural lesions within the oral cavity. The tongue, particularly its anterior two-thirds, is the primary site of occurrence, although they can also be found in other areas such as the buccal mucosa, lips, gingiva, palate, and alveolar ridge [10].

Oral neurofibromas vary in prevalence between adults (3.4-92%) and children (40%) [11-13]. Common sites include the tongue (26%), buccal mucosa (8%), alveolar ridge (2%), labial mucosa (8%), palate (8%), gingiva (2%), as well as the nasopharynx, paranasal sinuses, larynx, floor of the mouth, and salivary glands [14]. Enlargement of the fungiform papillae on the tongue is the most commonly reported finding [15]. Most patients are diagnosed before the age of 45, although NF1 can affect individuals of all ages, with a slightly higher prevalence in females. In a case reported by Almeida JM *et al.* (2017), a male patient presented with an oral neurofibroma on the posterior region of the tongue, characterized by slow growth and a sessile insertion. The clinical and histopathological features were consistent with NF1 and oral neurofibromas. Early diagnosis and appropriate management of NF1 are crucial to monitor disease progression and implement suitable treatment strategies. Overall, this case emphasized the significance of considering NF1 in the differential diagnosis of oral neurofibromas, especially in patients exhibiting multiple skin manifestations. Raising awareness of NF1 and its oral manifestations is vital for early identification and management of this uncommon genetic disorder [10].

Neurofibromas in the hand typically appear near flexion creases and cutaneous nerves. Cutaneous neurofibromas are often identified after excision of a solitary lesion in adults without a family history of neurofibromatosis. These hand masses may be flesh-colored or hyperpigmented papular nodules, leading to localized pain or peripheral nerve dysfunction. Boyd et al. described a technique involving pressure application to invaginate the lesion, which may be less effective in the hand due to the unyielding fascia of the glabrous palm and extensor tendons on the dorsal surface [16].

A previously reported case also presented a similar lesion which had a slow-growing, asymptomatic nodule on his tongue, surrounded by intact mucosa. Physical examination revealed numerous soft-consistency nodules on various skin areas, along with café-au-lait skin macules [10]. Nafarzadeh S *et al*. (2013)[17], Roy P *et al*. (2015)[18], Broly E *et al*. (2019)[19], and Buchholzer S *et al.* (2021)[20] also presented cases of male patients with neurofibromas, further adding to the understanding and documentation of this condition. These case reports emphasize the importance of considering neurofibromas in the hand when evaluating patients with soft-tissue masses, particularly in the context of neurofibromatosis type 1. Early diagnosis and appropriate management are crucial for providing effective treatment and ensuring favorable patient outcomes. Regular follow-up is essential to monitor for any signs of recurrence and address potential complications.The present case report was observed in a middle-aged female patient which was similar to case that was reported by Marcos JAG *et al.* (2007)[12] and Sheejith M *et al.* (2014) [15].

Neurofibromatosis type 1 (NF1) results from genetic alterations in the NF1 gene, located on chromosome 17q11.2. These mutations lead to increased cell proliferation and tumor development [21]. NF1 commonly presents with pigmented lesions, such as café au lait spots and freckles, appearing early in childhood or at birth [13,21-23]. Café au lait spots are hyperpigmented macules of varying shades, typically not found on the face, while inguinal and axillary freckles (Crowe's sign) are also frequently observed [21]. The reported case showed multiple café au lait spots, bilateral axillary and inguinal freckles, along with skin neurofibromas and angiomas, characteristic of NF1 [13,21]. Localized neurofibroma is the most common form in NF1, developing along peripheral nerves as focal masses with well-defined margins, often appearing later in childhood or early adolescence, and increasing in number with age. NF1 may also affect other organs, including the stomach, bowels, kidney, urinary bladder, larynx, and heart. The head and neck are commonly involved, with sites like the scalp, cheek, neck, and oral cavity being affected [21]. Bone involvement in NF1 may result from external resorption due to neurofibroma pressure, as observed in the case. Bone malformations, like kyphoscoliosis or pseudoarthrosis, may occur, and the temporomandibular joint (TMJ) can also be affected [23-25]. Skeletal involvement is seen in almost 40% of NF1 patients, with scoliosis being the most common pathology [13,25]. Radiological findings in oral neurofibromas may include widening of the mandibular channel, mandibular foramen, and mental foramen [21,23]. Histologically, neurofibromas consist of Schwann cells, perineural cells, and endoneural fibroblasts and lack a capsule. Schwann cells predominate and can be highlighted with various staining techniques [24]. Immunohistochemical staining of neurofibromatosis type 1 (NF1) with S100 protein is commonly used to identify the presence of Schwann cells, which are characteristic of neurofibromas. Additionally, KI 67 staining is utilized to assess the proliferative activity of the tumor cells, aiding in the evaluation of tumor aggressiveness and growth potential.SOX 10 can be used to rule out schwannoma from neurofibromatosis type 1 (NF1) due to its specificity as a marker for Schwann cells. In cases where neurofibromas are suspected, positive SOX 10 staining indicates the presence of Schwann cells, supporting the diagnosis of neurofibromas over schwannomas, which typically do not express SOX 10. Neurofibromatosis-related tumors, such as schwannomas, can be differentiated from neurofibromas based on their distinct immunohistochemical characteristics. Schwannomas demonstrate a strong and diffuse expression of S100 protein, with predominant spindle cells displaying Schwann cell differentiation. Additionally, most schwannomas also exhibit positive staining for SOX-10, providing a valuable marker for distinguishing them from other neurofibromatosis-associated lesions. However, caution should be exercised, as occasional atypical expressions of other markers like cytokeratins, desmin, and TTF-1 may be observed in schwannomas, and the mosaic expression pattern of INI1 can aid in differentiating schwannomas associated with different types of neurofibromatosis from sporadic cases [26-28]. Neurofibromatous lesions generally progress slowly without causing pain, though growth may accelerate during periods like puberty or pregnancy. Understanding the clinical, radiological, and histological characteristics of neurofibromas in NF1 is vital for accurate diagnosis and effective management of this complex genetic disorder [12].

Treatment for neurofibromatous lesions involves total or partial resection, waiting until growth is completed to reduce recurrence risk. Total resection with 1 cm margins is preferred for accessible and small tumors. Avoid radiotherapy or chemotherapy; use Thalidomide for pain in plexiform neurofibromas. Surgery does not promote malignant transformation; rate is 3-5% in NF1-related neurofibromas. NF1 patients need genetic counselling due to autosomal dominant inheritance (50% likelihood of transmission). Malignant transformation to neurofibrosarcoma carries poor prognosis, 15% 5-year survival with frequent metastases. Recurrence risk increases with multiple recurrences. Oral surgeons and dentists should consider NF1 when encountering characteristic oral lesions, monitoring for complications, especially malignant transformation [12].

CONCLUSION

In conclusion, this case report highlights the importance of early recognition and appropriate management of neurofibromatosis type 1 (NF1) with oral manifestations. Oral neurofibromas are a rare but significant finding in NF1 patients, affecting various sites within the oral cavity. Surgical resection remains the treatment of choice for addressing aesthetic and functional concerns, with Thalidomide showing promise in

managing pain associated with plexiform neurofibromas. Genetic counselling is crucial for NF1 patients due to its autosomal dominant inheritance, emphasizing the need for long-term follow-up to monitor potential complications and malignant transformation. Oral and maxillofacial surgeons, as well as dentists, play a vital role in early diagnosis and comprehensive care for patients with NF1. Increased awareness and prompt intervention can improve patient outcomes and quality of life, ensuring a better understanding and management of this complex genetic disorder. Further research and collaborative efforts are warranted to advance our knowledge and optimize the management of NF1 and its associated oral manifestations.

Conflicts of Interest

The author reports no conflicts of interest.

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