Oral Medicine Case Book 47: Oral neurofibroma

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CASE REPORT

A 29-year-old male patient presented at the Oral Medicine Clinic with the complaint of slow-growing growths on his tongue, causing discomfort. Extra-oral examination revealed several painless soft tissue nodules on his face (Figure 1 and 2), trunk (Figure 3), back (Figure 4) and arms. The patient reported that the lesions had appeared during childhood and had since increased in size and number. He was unaware of any family history of the disease. Intra-oral examination showed two soft tissue nodules on the midline of the dorsal surface of the tongue, 3,5cm and 0,5 cm in diameter respectively (Figure 5).

An excisional biopsy of the smaller nodule was performed and the specimen submitted for histopathological evaluation. A 0.2% aqueous solution of chlorhexidine digluconate was prescribed as antibacterial mouthwash. The patient was instructed on the management of possible postoperative bleeding and asked to return to the clinic a week later for suture removal.

DIAGNOSIS AND MANAGEMENT

Histological examination revealed an ill-defined benign cellular neoplasm consisting of bland short fusiform or rounded Schwann cells in a fine fibrillary collagenous background. The lesion exhibited an infiltrative growth, with extension along the connective tissue septa and between fat cells and skeletal muscle fibres (Figures 6 and 7). The lesional Schwann cells stained positively for S-100 protein (Figure 8). The histopathological diagnosis of an incompletely excised neurofibroma (diffuse type), together with the characteristic clinical features and history, led to a final clinical diagnosis of neurofibromatosis.[1]

At the next visit the diagnosis was conveyed to the patient and he was referred to the Department of Oral and Maxillofacial Surgery for the removal of the residual tongue lesions, and the Dermatology Clinic for further investigation and management of the skin lesions.

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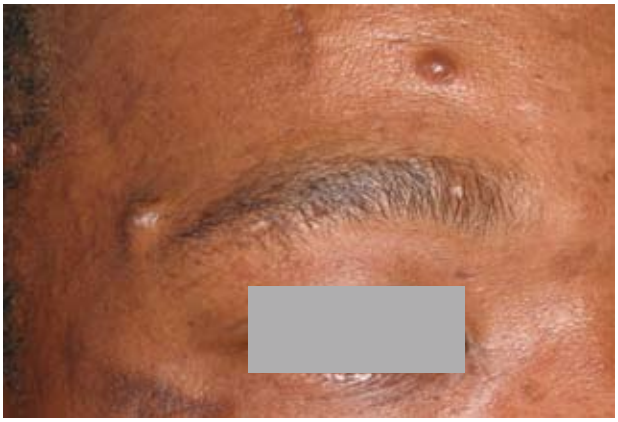

Figure 1: The patient presented with multiple nodules on the forehead and around the eye.

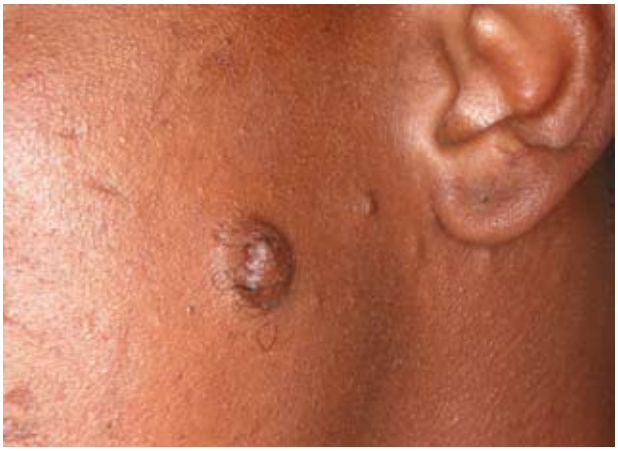

Figure 2: A large nodule and several smaller ones were present on the left preauricular region.

DISCUSSION

Neurofibromas are fairly common, benign neoplasms of peripheral nerves, usually presenting as solitary lesions of the skin, mostly on the head and neck but occasionally on mucosal surfaces. Localised or solitary neurofibromas are often seen in patients who are otherwise healthy. A diagnosis of neurofibromatosis type 1 (NF1) should be considered if a patient presents with oral mucosal neurofibromas and concomitant multiple skin lesions. NF1 is the most common form of neurofibromatosis and is also known as von Recklinghausen's disease, eponymously named after a 19th century German pathologist (1833-1910). NF1 is a reasonably common, dominantly inherited condition with high pen-

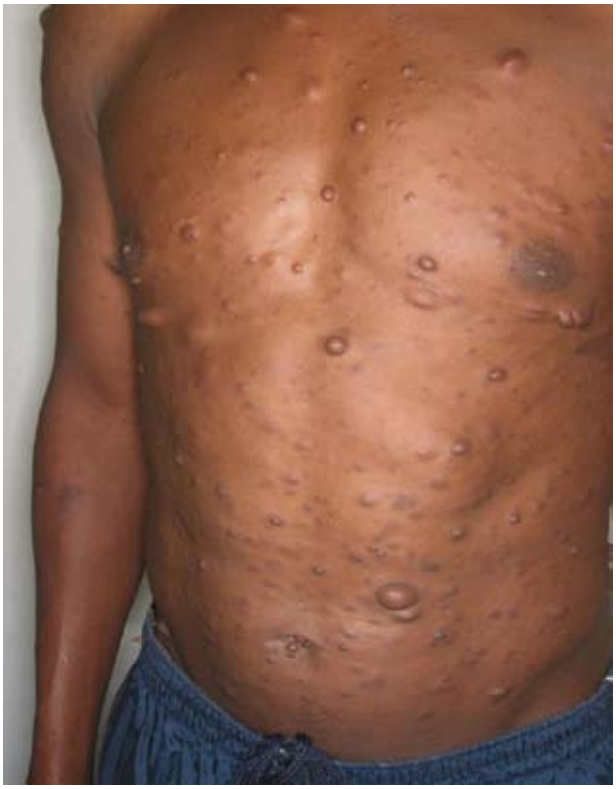

Figure 3: Multiple cutaneous and subcutaneous nodules were present on the trunk and arms of the patient.

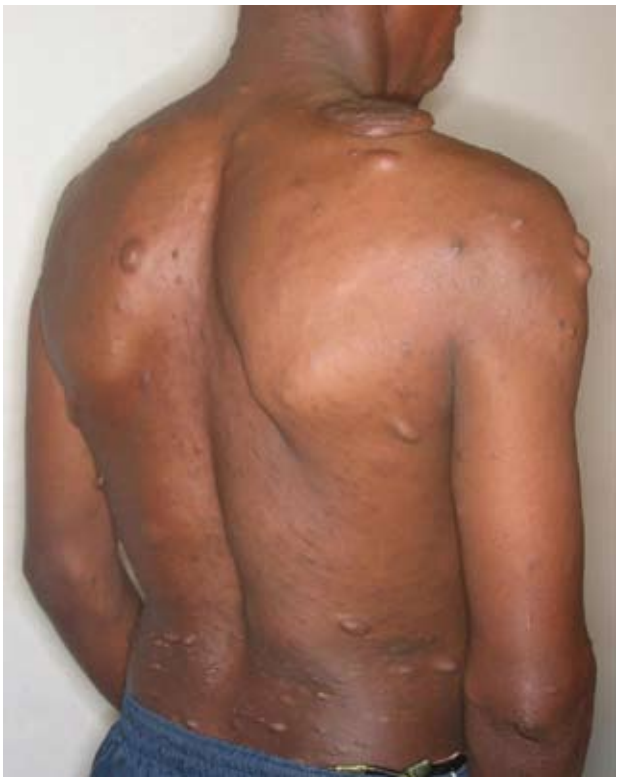

Figure 4: A large number of cutaneous and subcutaneous nodules were present on the back and arms of the patient. Note the large growth on the patient's right shoulder.

etrance and variable expression. Several different clinical variants of the disorder have been described. The condition is caused by a defect in a large gene on chromosome 17 that expresses a tumour suppressor protein, Neurofibromin 1, which inactivates the Ras oncogene. The loss of NF1 gene expression therefore results in increased Ras activity, cell proliferation and uncontrolled growth of cells of the

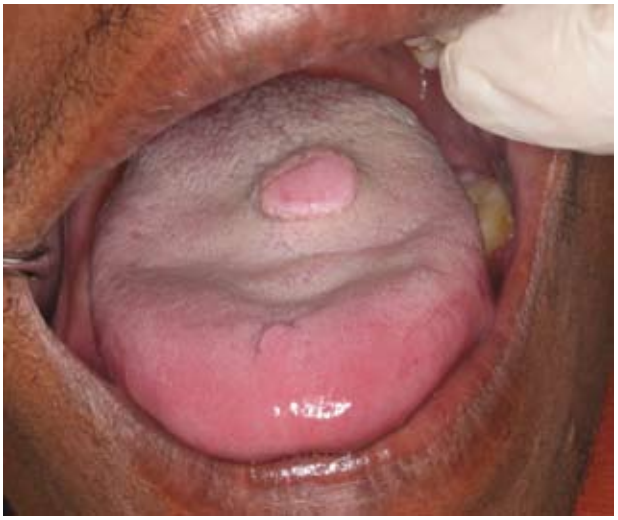

Figure 5: Two soft tissue nodules covered by normal oral mucosa were present on the dorsal surface of the tongue. Unlike the smaller nodule, the larger nodule is raised with well-defined borders.

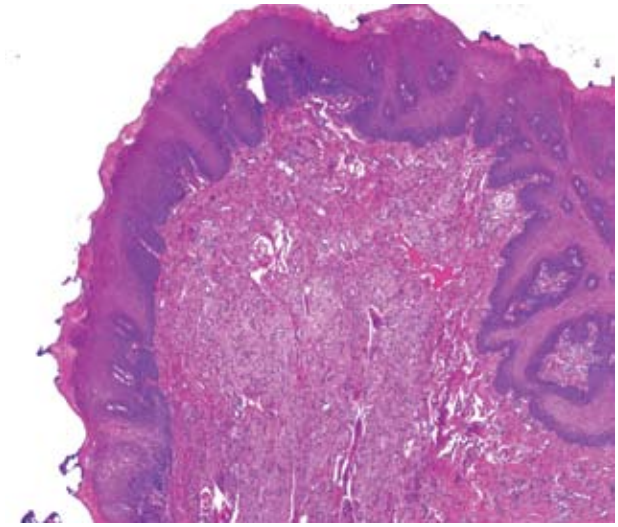

Figure 6: This photomicrograph illustrates a nodule covered by parakeratinising stratified squamous epithelium (H & E, x40).

neural crest, i.e. Schwann cells, melanocytes and endoneurial fibroblasts. The resultant uncontrolled growth produces tumours throughout the body together with disorders of skin pigmentation, including the development of *café-au-lait* spots. The Neurofibromin 1 gene is a large gene with many homologous regions and is thus predisposed to developing mutations. Neurofibromatosis type 1 affects approximately one in every 3000 individuals in many populations worldwide. Only half of the patients with this disease have affected family members with the remaining 50% of cases of NF1 arising from *de novo* germ-cell mutations.[1, 4]

A diagnosis of NF1 can be made when two or more of the following clinical features are present: six or more *café-au-lait* macules, axillary or inguinal freckling, two or more neurofibromas of any type or one plexiform neurofibroma, optic glioma, two or more Lisch nodules (iris hamartomas), a distinct osseous lesion such as sphenoid dysplasia or pseudoarthrosis or thinning of the long bone cortex, and a first-degree relative with NF1 by the above criteria.[1, 2] Neurofibromatosis type 2 (NF2) is another variant of neurofibromatosis and is the result of a mutation in the NF2 gene on chromosome 22. The main feature of this condition is bilateral schwannomas affecting the eighth cranial nerve. It is estimated that the condition affects one in every 25000 individuals worldwide.[2]

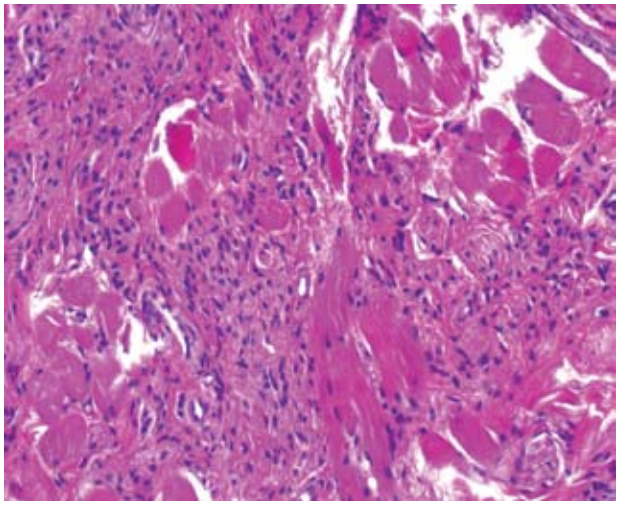

Figure 7: This photomicrograph shows infiltration of skeletal muscle fibres by a cellular neoplasm composed of short fusiform or rounded Schwann cells with darkly-stained nuclei in a collagenous background (H & E, x200).

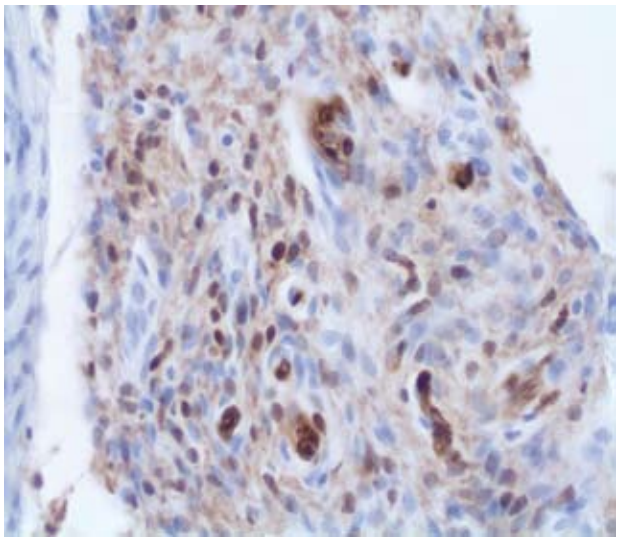

Figure 8: This photomicrograph shows the positive brown staining for S100 protein in the lesional Schwann cells (x 400).

Studies indicate that oral lesions are present in approximately 75% of all cases of NF1 and there is a strong association between NF1 and tongue neurofibromas.[1,4] Neurofibromas commonly affect young adults and initially present as slow-growing, soft, painless lesions that vary in size from small nodules to substantial tissue masses.[4] Commonly affected intra-oral sites include the tongue, buccal mucosa, alveolar ridge, gingivae, lips, palate, floor of mouth and the pharyngomaxillary space.[2] The majority of lesions affecting the tongue are nodular in nature but, at times may present as macroglossia. Symptoms associated with tongue lesions include discomfort and pain. If the base of the tongue is involved, it may also include odynophagia, dysphagia, voice changes and otalgia. The presence of a neck mass, tooth loss or impacted and malpositioned teeth are other signs frequently encountered in these cases.[1]

Pathologically, several types of neurofibroma occur with NF1. They are distinguished on the basis of their gross and microscopic features and include: localised neurofibroma, plexiform neurofibroma, diffuse neurofibroma and pigmented neurofibroma. A feature unique to all neurofibromas is the presence of Schwann cells in a fibrous to myxoid stroma. Diffuse neurofibroma is ill-defined and spreads between connective tissue elements (fat cells and skeletal muscle fibres). Despite its infiltrative growth, it does not destroy but rather envelops the native tissue structures.

The differential clinical diagnosis of a solitary neurofibroma includes other submucosal masses of connective tissue origin such as traumatic fibroma, granular cell tumour and lipoma. If a diffuse lesion is present, resulting in macroglossia, the differential diagnosis should also include lymphangioma and amyloidosis.[5] Solitary neurofibromas usually run a benign clinical course with a low frequency of recurrence after surgical removal, however, the multiple and larger lesions commonly found in NF1, have a higher recurrence rate. Currently there is no specific therapy for NF1. Although lesions can be removed surgically, the presence of numerous larger lesions may make this approach impractical.[3,4,5] Extensive facial lesions that need to be removed for cosmetic reasons usually respond well to carbon dioxide laser ablation or dermabrasion.[4]

Malignant transformation of neurofibromas may occur but the incidence of this complication is low with only 2%-6% of patients with NF1 developing malignancies. This association is however, greater with plexiform neurofibromas. The development of malignant peripheral nerve sheath tumour is reported to be the leading cause of cancer-related deaths in patients with NF1, with a 5-year survival rate of 15%.[1, 4] A sudden increase in the size or appearance of a neurofibroma should alert the attending clinician to the possibility of malignant transformation.[1]

CONCLUSION

The case presented above is typical of NF1, both in terms of its clinical presentation and histopathological features. NF1 is often a dominantly inherited condition but since the patient had no family history of NFI, it can be assumed that he was one of the approximately 50% of cases where the condition is the result of a *de novo* germ cell mutation. Patients with NF1 should be counselled by an appropriately-trained professional, particularly if the patient is still in his or her productive years. It should also be kept in mind that oral mucosal neurofibromas may cause discomfort and, when enlarged, may interfere with speech and mastication. For that reason, symptomatic oral lesions are diagnosed more regularly than early painless lesions and clinicians should include neurofibromas in the differential diagnosis when investigating any oral mucosal nodules. Histopathological and immunohistochemical evaluation will make an early diagnosis possible and could be of immense benefit to a person suffering from this potentially debilitating condition.

Declaration: No conflict of interest was declared

References and *recommended reading

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