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Non Syndromic Solitary Neurofibroma of the Oral Cavity- Report of Two Rare Cases with Review of Literature

Running title- Solitary Neurofibroma

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KEYWORDS

Oral Neurofibroma, Neurofibromatosis Type 1, Peutz-jeger syndrome, café au lait pigmentation, immune-histochemistry, histopathological examination..

ABSTRACT:

Introduction- Neurofibroma is a benign tumor originating from the peripheral nerve sheath, commonly involving Schwann cells, perineurial cells, and fibroblasts. While neurofibromas frequently occur in association with Neurofibromatosis Type 1 (NF1), solitary neurofibromas can also manifest independently. Oral neurofibromas are rare, with fewer than 30 cases reported, most often involving the tongue, palate, and buccal mucosa.

Case Series- This paper presents two case reports of solitary oral neurofibromas: a 35-year-old female with a growth in the mandibular gingiva and a 13-year-old female with a lesion on the palate. Both cases presented as slow-growing, painless masses, and diagnosis was confirmed through histopathological examination and immunohistochemical staining (S-100, CD34). Surgical excision was performed, and post-operative recovery was uneventful with no recurrence after 8 and 11 months, respectively.

Conclusion- Neurofibromas pose diagnostic challenges due to their resemblance to other oral lesions like pyogenic granuloma or peripheral ossifying fibroma. However, accurate diagnosis using imaging and immunohistochemistry aids in effective treatment planning. While malignant transformation is rare, particularly in isolated cases, close monitoring is necessary to manage potential complications. The favorable prognosis post-surgical excision underscores the importance of early identification and management of oral neurofibromas.

Introduction

Neurofibroma is a benign tumor originating from peripheral nerve sheath cells, including Schwann cells, perineurial cells, and fibroblasts.[1]It is one of the most common peripheral nerve tumors, with a frequency of approximately 6.5% in the oral cavity. These tumors can manifest as solitary lesions or as part of neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, a genetic disorder caused by mutations in the NF1 gene.[2] Clinically, oral neurofibromas typically appear as discrete, non-tender, submucosal masses, with common locations being the tongue, buccal mucosa, and posterior mandible.[3]

Neurofibromas can be classified into two main types: dermal and plexiform (WHO). Dermal neurofibromas arise from a single peripheral nerve, while

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plexiformneurofibromas involve multiple nerve bundles, often leading to poorly circumscribed and locally invasive tumors. These tumors can cause significant morbidity and disfigurement, and their treatment generally involves surgical excision.[4]

Histologically, neurofibromas are composed of spindle-shaped cells with scant cytoplasm, embedded in a matrix that varies in mucin and collagen content. The cells in neurofibromas show differentiation towards Schwann cells, perineurial cells, and fibroblasts.[5]Immuno-histochemical analysis is often used to confirm the diagnosis by identifying these cell types.[6]

Neurofibromas are the hallmark of neurofibromatosis, but solitary lesions can occur independently of the syndrome. These solitary neurofibromas are typically localized and are not associated with systemic or hereditary factors.[7]Most solitary oral neurofibromas occur in adults, but they can also affect children. There is no specific age predilection for their occurrence, although they are more commonly diagnosed in young adults.[8]

In the oral cavity, neurofibromas commonly affect the tongue and buccal mucosa, with around 20-60% linked to NF-1.[7]Solitary neurofibromas without association to NF1 are even rarer, and their clinical diagnosis can be challenging due to their similarity to other oral lesions such as papillomas, fibrous hyperplasia, and schwannomas.[9]

Surgical excision is the preferred treatment for neurofibromas, especially for localized lesions. Recurrence is rare, but plexiformneurofibromas, due to their diffuse nature, can be more challenging to completely remove, leading to potential re-growth.[10] Malignant transformation is also a risk, particularly in patients with NF1, where neurofibromas may evolve into malignant peripheral nerve sheath tumors.[8, 11]

Herein, we report two cases of solitary neuro-fibroma in the oral cavity which were initially confused as peripheral tumors.

Case report-

Case 1- A 35 years old female patient reported to the OPD of a tertiary care centre in Siliguri with chief complaint of a painless growth in the lower front teeth region that has been gradually increasing in size over the last 5 years. (Fig 1) She gave history of sudden onset of the growth, associated with mild discomfort due to reduced space for tongue movement. She had no relevant medical or drug or habit history and the growth was not associated with any history of fever or pain or loss of sensation in that region.

On intra-oral examination, a well-defined solitary growth measuring 3x2 cm in diameter could be appreciated involving the lingual gingiva of central incisor extending up-to the second premolar in the third quadrant. (Fig 2)The growth was closely associated with the lingual frenum and the floor of the mouth but free from both. The surface of the growth appeared smooth, devoid of any ulcerations or discharge. The growth was also associated with few foci of erythematous areas secondary to localized micro-trauma. The overall oral hygiene of the patient was poor with grade 2 stain and calculus. On palpation, the growth was soft to firm in consistency, fluctuant and fleshy, non-tender with a sessile base, and the other inspector findings were confirmed. The growth was not associated with any bleeding tendencies and the regional lymph nodes were not appreciable.No mobility of the regional tooth could be appreciated. A cone beam computed tomography (CBCT) was advised that revealed no bony involvement of the lesion. (Fig 3)

A differential diagnosis of Pyogenic Granuloma, Peripheral Giant cell granuloma (PGCG) and peripheral ossifying fibroma (POF) was given. After obtaining written patient consent, an incisional biopsy was done and sent for histo-pathological evaluation. The H & E stained section of the specimen revealed the presence of neuron-like or spindle cells. Some of the spindle cells are with buccal nucleus while some are with wavy nucleus. The connective tissue stroma has evidence of carrot shredded collagen fibres with mast cells, some mast cells were in degranulation stage. (Fig 4)Immuno-histochemistry (IHC) was also done for this particular case, and IHC was positive for S-100 and CD-34, indicating that the growth has a nervous and endothelial origin. (Fig 5)

Final diagnosis of Solitary Neurofibroma was given. The growth was excised surgically and the healing of the patient was uneventful.

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Case 2- A 13 year old female patient reported to the OPD with chief complaint of a painless growth in the upper palate on the right side that has been gradually increasing in size since last 1 year. (Fig 6) She gave history of sudden onset of the lesion with no pain or burning sensation. She complained of some degree of discomfort due to the growing lesion at the time of swallowing, otherwise growth was not associated with any history of fever or loss of sensation in that region. She had no positive medical or habit or drug history.

On intra-oral examination, a diffuse solitary growth measuring 4x3 cm in diameter is noted in the right palate crossing the midline involving the palatal mucosa extending antero-posteriorly from the incisive papilla up-to the junction of the hard and soft palate, and terminating at the soft palate. (Fig 6) The surface of the lesion appeared smooth with stretched out palatal mucosa, free from any ulcerations or discharging sinuses. The overall oral hygiene of the patient appeared good with the presence of only mild stains. On palpation, the growth was soft and fluctuant in consistency, non-tender with a sessile base. Regional tooth mobility or lymphadenopathy was absent. Computed Tomography (CT) of the paranasal air sinuses were done that revealed the presence of a rounded well defined soft tissue space occupying lesion along the medial half of the palate on the right abutting the alveolar process of the maxilla. CT revealed evidence of local palatal bone re-modeling but no frank bone destruction could be appreciated. The lesion appeared localized without extension into the maxillary antrum or nasal cavity. (Fig 7)

A provisional diagnosis of POF and PGCG was given. An incisional biopsy was performed from the lesion after obtaining patient consent. The H & E stained section of the specimen revealed similar findings as the previous case. An added feature noted exclusively in the second case was the presence of deformed palatal salivary glands due to localized pressure from the proliferating spindle cells or neural cells. (Fig 8)IHC was done to confirm the positivity for S-100. (Fig 9)

A final diagnosis of Solitary Neurofibroma was given. Surgical excision of the lesion was done and the post-operative healings were uneventful.

Since the two patients reported at different time frame, their follow up was also done at 8 months and 11 months respectively.During each follow up, both the patients were assessed intra-orally and extra-orally for any evidence of recurrence. In either case, nopathology could be appreciated and both the patients exhibited satisfactory healing of the biopsy site.

Discussions

Neurofibromas are benign tumors originating from the sheaths of peripheral nerves, rarely found in the head and neck area. Composed primarily of Schwann cells and perineural cells within a collagen matrix,[12] these tumors may manifest as either solitary growths in non-syndromic cases or multiple growths associated with genetic disorders like neurofibromatosis or type III multiple endocrine neoplasia (MEN III). Neurofibromas are classified as either myxomatous or plexiform, each with different tissue distributions and characteristics.[13]

Most neurofibromas are asymptomatic but may cause sensory disruptions depending on the nerve affected.[14] Diagnosing intra-oral neurofibromas can be challenging due to their similarity with other benign and malignant lesions, such as lipomas, fibromas, and salivary gland tumors.[15] Histologically, neurofibromas are unencapsulated, comprising spindle cells within a myxoid matrix, with Schwann cells that test positive for the S-100 protein, a distinguishing marker.[16] Variations in tumor composition, such as fatty deposits, can further complicate diagnosis. Some neurofibromas, termed lipomatousneurofibromas, contain fat cells, potentially causing diagnostic confusion with spindle-cell lipomas.[17]

Oral neurofibromas have an estimated incidence of 4-7% in neurofibromatosis type 1 (NF-1) cases, affecting around 1 in 3,000 to 4,000 people. Oral cases are uncommon, and among them, the tongue is the most frequent site.[18] Most arise from branches of the fifth cranial nerve, with lingual nerve involvement being rare. Typically, these tumors appear as slow-growing, painless submucosal masses, rarely associated with neurological symptoms.[19]

Isolated neurofibromas on the palate are particularly rare, presenting as nodular, mobile, and occasionally discomforting if nerve compression occurs.[12]Although imaging may be used to assess tumor extent, traditional histological examination often suffices. Typical diagnostic markers include Schwann cell proliferation

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and perineural cell presence in a myxomatous or microvacuolated stroma.[7] Differentiating neurofibromas on the hard palate from other lesions, especially minor salivary gland tumors, is crucial.[20]

This case series includes two unique oral neurofibroma presentations: one on the hard palate and another on the lingual gingiva. The latter is an especially rare site for a solitary neurofibroma, potentially the first reported case. Clinical presentation for both cases involved a slow-growing, painless mass with firm attachment to underlying structures but no bone involvement. While solitary oral neurofibromas are common on the tongue, buccal mucosa, sub-mandibular glands, mandible etc (Table 1), this is probably the first reported case of solitary neuro-fibroma on the lingual gingiva. A 2019 review by Broly et al. examined 26 cases of isolated oral neurofibromas, highlighting the rarity of these tumors in the oral cavity.[4]

Magnetic resonance imaging (MRI) is preferred for evaluating these tumors, though computed tomography (CT) was used here to determine lesion depth and exclude bone involvement. MRI images reveal neurofibromas as low to intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted images, helping to distinguish the tumor's fibro-collagenous and myxoid components. Differentiating neurofibromas from other similar lesions, such as schwannomas or hemangiomas, remains challenging, though imaging aids diagnosis.[11, 15]

A key distinction between solitary neurofibromas and those related to neurofibromatosis lies in the boundary with surrounding tissues.[3] While both may lack a capsule, achieving clear resection margins is harder without one. In this case series, excision was completed from both the mucosal surface and deeper periosteal layers, with care to preserve anatomical structures.[8] Immunohistochemistry, particularly S-100 and CD34 staining, aided in accurate diagnosis for one patient, while histopathology alone sufficed for the other.[21]

Though rare, malignant transformation of neurofibromas into sarcoma can occur, especially in syndromic cases like Von Recklinghausen's disease or MEN III.[22] Surgical excision generally has a favorable prognosis, with low recurrence rates and minimal complications. Complete removal, however, can be challenging if the tumor intertwines with regional nerves.[2, 3]In this series, both lesions were excised with wide margins, with no recurrence observed to date. Solitary oral neurofibromas have a low recurrence rate, but multiple recurrences may increase malignancy risk.[23]

Conclusion

This is probably the first reported case of an intra-oral solitary neuro-fibroma on the lingual gingiva and among a very few reported cases of such lesion on the hard palate. Non syndromic solitary neurofibromas are clinically distinct entities, about which very little is known due to limited number of reported cases in literature. This paper highlights the various clinical, radiological and histo-pathological features of the reported cases of solitary oral neuro-fibroma reported till now, including the present two cases, which had corroborating features. It is important to consider solitary neurofibromas in the differential diagnosis of any hyperplastic peripheral lesion where the signs of trauma are not conspicuous.

Table 1 showing the list of reported cases of oral neuro-fibroma-

SL NO	Year	Authors	Age/Sex	Location	Clinical features	Diagnostic tools	Treatment	Outcome
1.	2021	Singh et al[9]	35/F	Floor of the mouth	Painless swelling	MRI, Histopathology	Surgical excision	No recurrence after 1 year
2.	2020	Chen et al[11]	42/M	Tongue	Slow growing painless mass	MRI, Histopathology, S-100	Surgical excision	No recurrence after 6 months
3.	2019	Lopez et al[13]	16/F	Buccal mucosa	Painless nodule	MRI, Histopatholgy	Surgical excision	No recurrence after 2 years
4.	2018	Patel et	30/M	Submandibular	Mobile,	MRI,	Surgical	No

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		al[15]		gland	painless mass	Histopathology, S-100	excision	recurrence after 18 months
5.	2017	Kim et al[17]	22/F	Posterior mandible	Painful swelling, paresthesia	CT, MRI, Histopathology	Surgical excision	No recurrence after 3 years
6.	2016	Hernandez et al[19]	40/F	Hard palate	Painless swelling	MRI, Histopathology, S-100	Surgical excision	No recurrence after 1.5 years
7.	2024	Present case	35/F 13/F	Lingual gingiva. Hard palate.	Painless slow growing soft fluctuant	CBCT, Histo-pathology, S-100, CD-34. CT, Histology.	Surgical excision	No recurrence after 8-11 months.

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Images

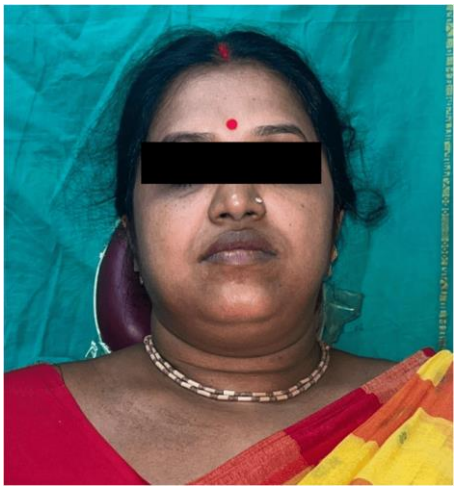

Figure 1 showing the extra-oral initial presentation of the patient (Case I).

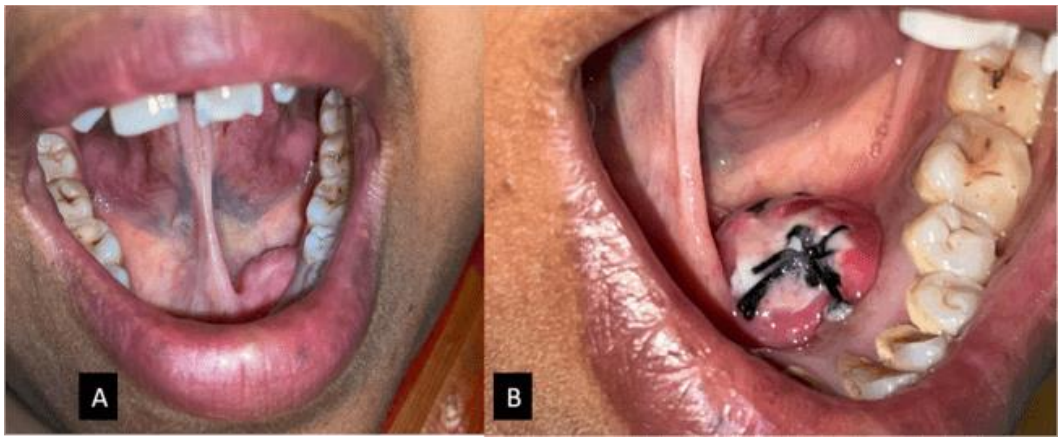

Figure 2(A) showing the intra-oral presentation of the patient (Case I), 2(B) is showing the post-operative presentation of the lesion after incissional biopsy.

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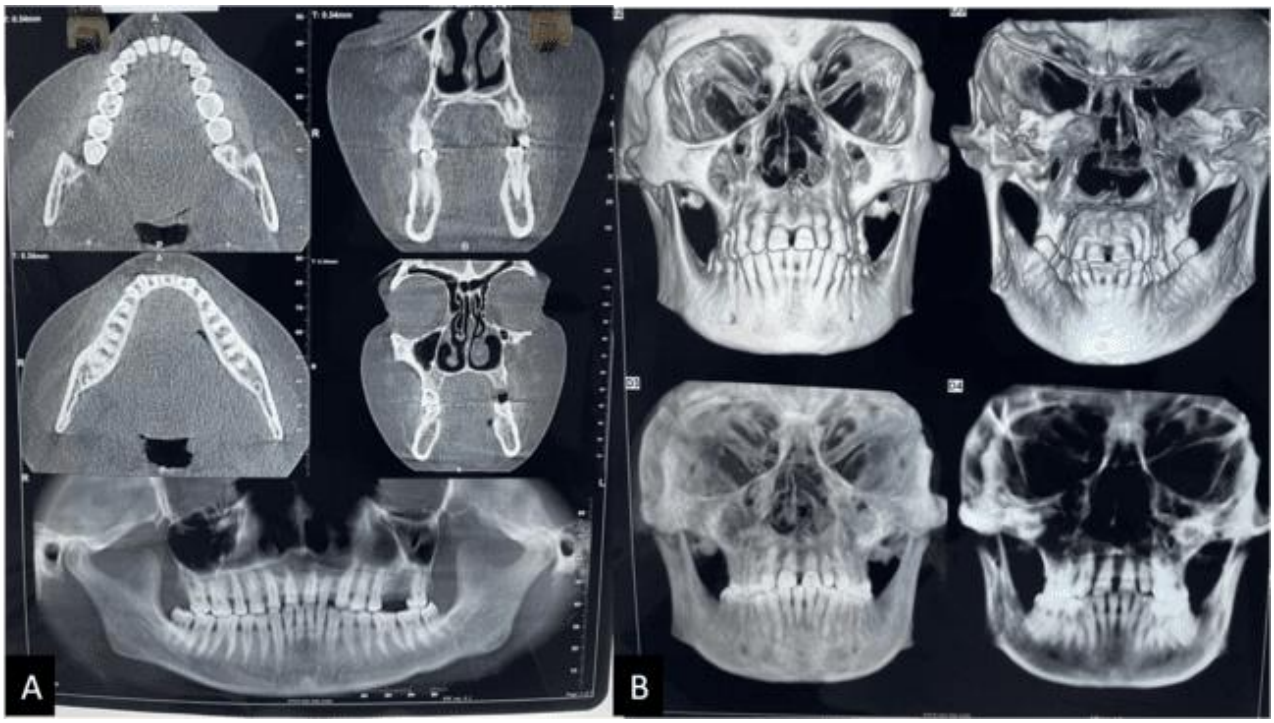

Figure 3 (A) shows the CBCT imagesand 3(B) shows the three dimensionally reconstructed image of the patient (Case I) highlighting that there is no bony involvement in the mandible at the site of the lesion.

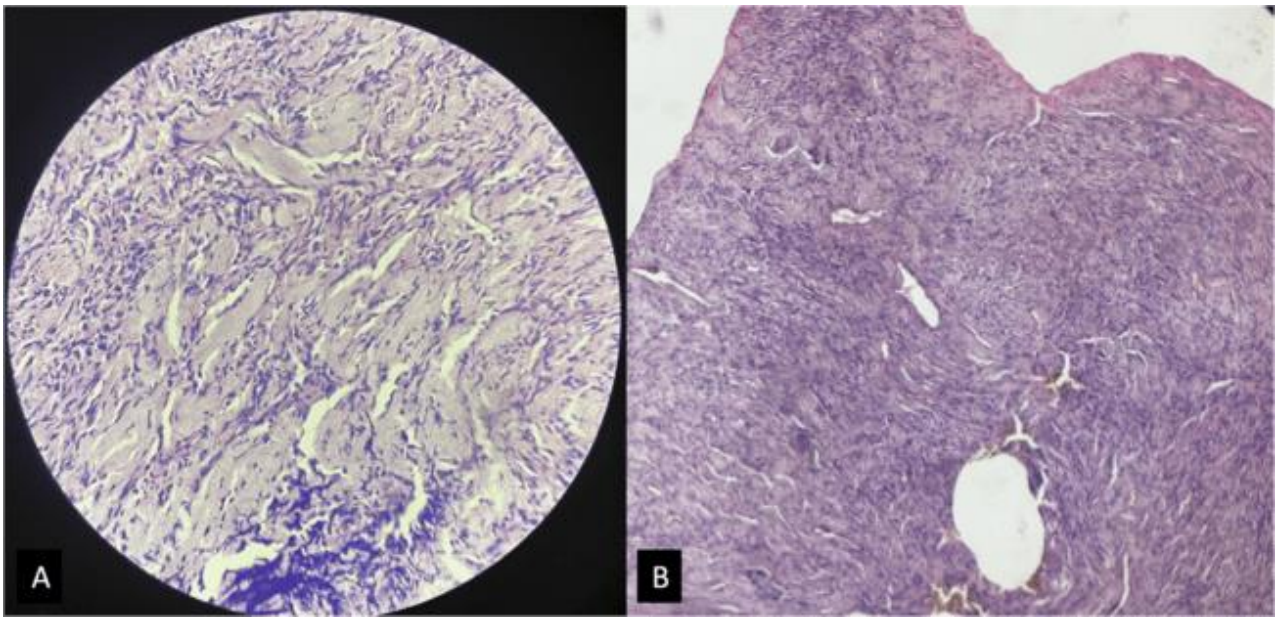

Figure 4 showing the photomicrograph of the H & E stained specimen (A-10X, B-4X) that reveals the presence of neurone-like or spindle cells. Some of the spindle cells are with buccal nucleus while some are with wavy nucleus. The connective tissue stroma has evidence of carrot shredded collagen fibres with mast cells, some mast cells are in degranulating stage.(Case I)

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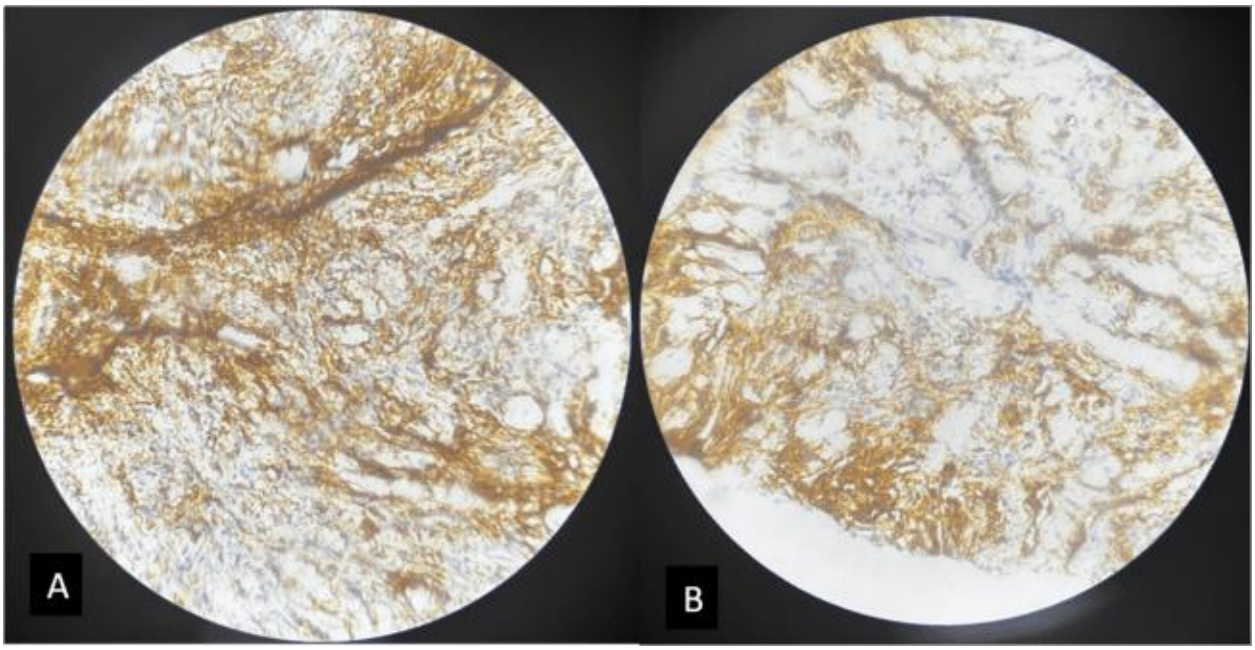

Figure 5 showing the photomicrograph of the specimen that stained positive for S-100 (A) and CD-34 (B) under 10X resolution. (Case I)

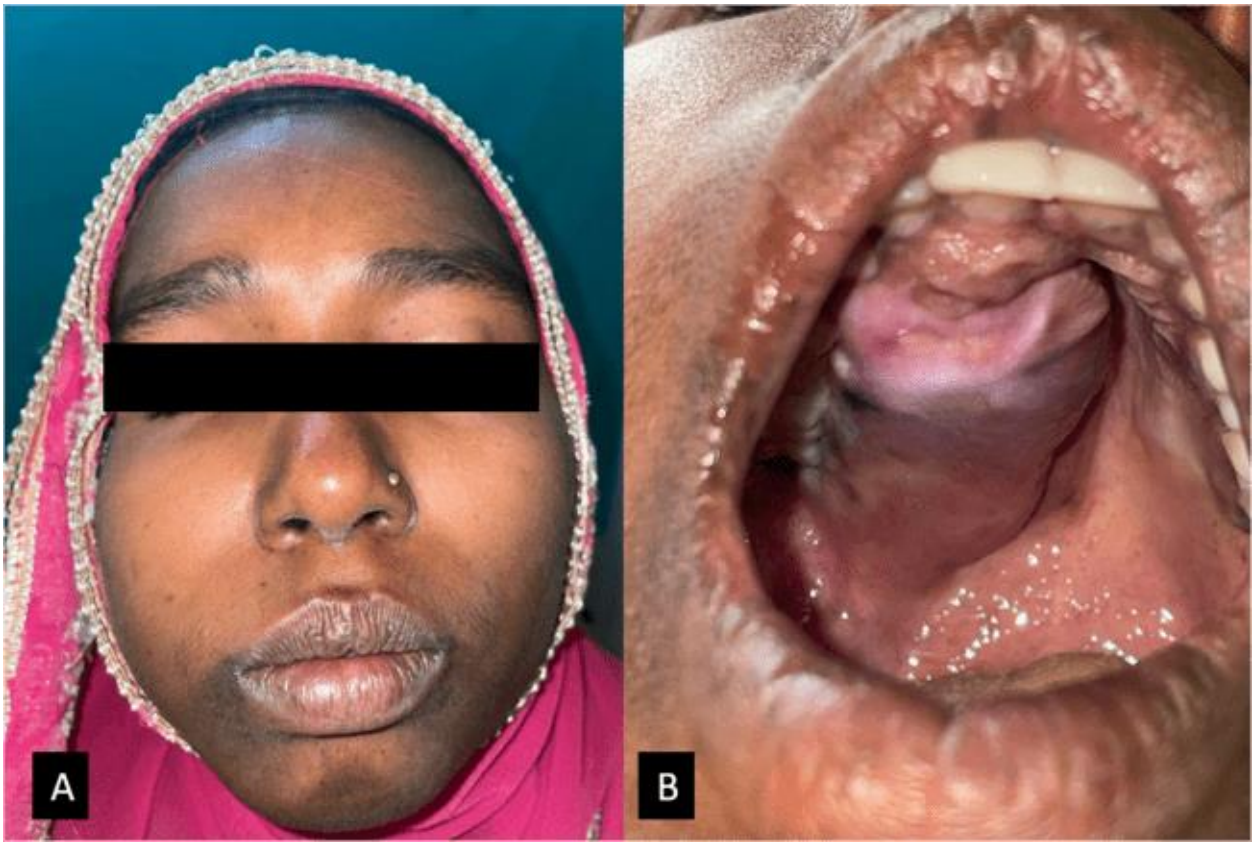

Figure 6 showing the initial extra-oral (A) and intra-oral (B) presentation of the patient (Case II)

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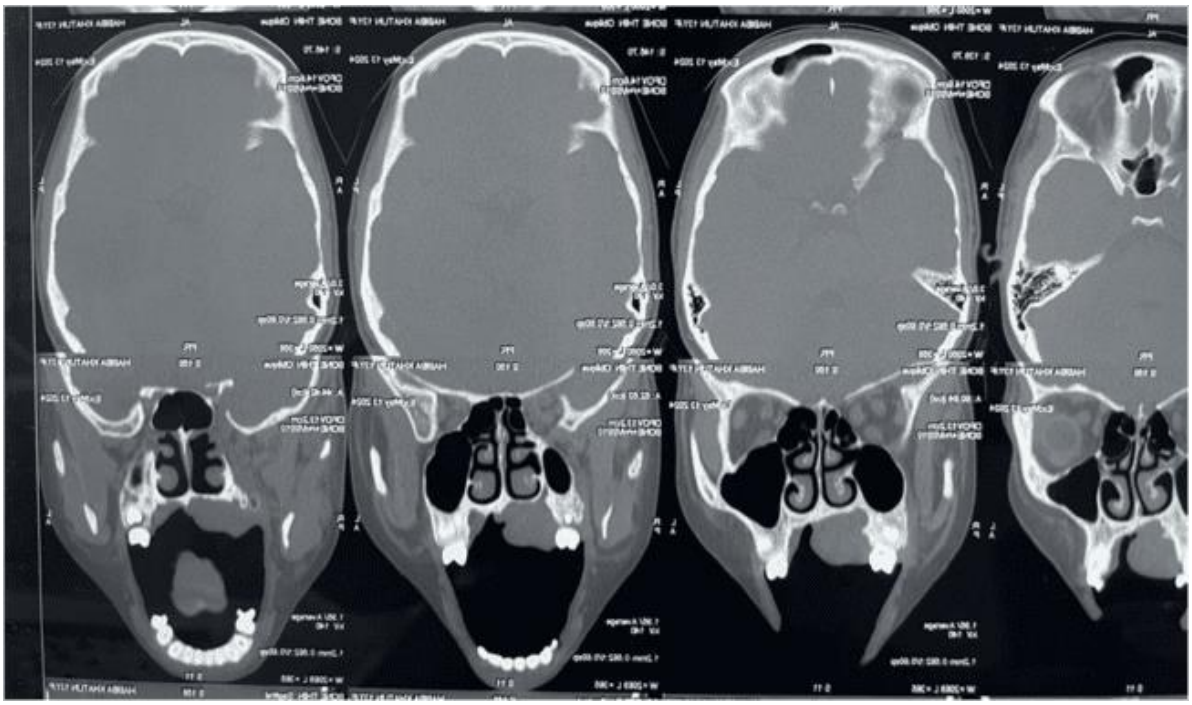

Figure 7 showing the CT images of the patient (Case II) that reveals the extent of the lesion on the right side of the hard palate, abutting the alveolar process of maxilla without any evidence of bone destruction or extension into the maxillary antrum or nasal cavity.(Case II)

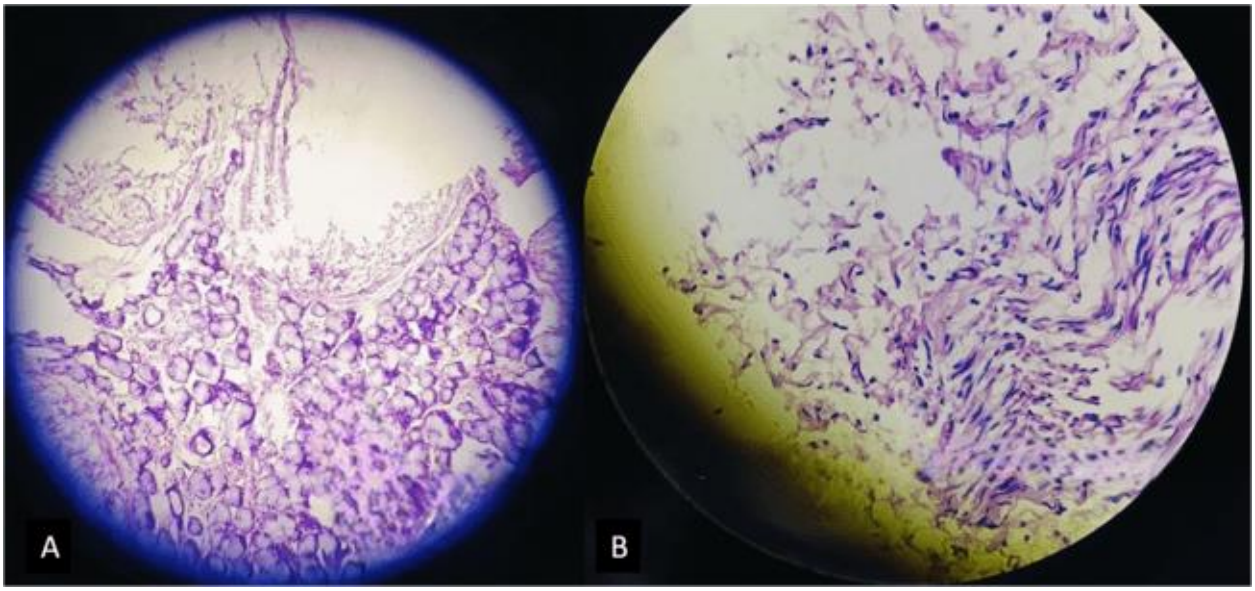

Figure 8A showing the photomicrograph of the H & E stained specimen (A-10X, B-4X) that reveals the presence of neurone-like or spindle cells. Some of the spindle cells are with buccal nucleus while some are with wavy nucleus. The connective tissue stroma has evidence of carrot shredded collagen fibres with mast cells (8B), some mast cells are in degranulating stage. The palatal salivary glands show deformity due to localized pressure from the proliferating spindle cells or neural cells. (Case II)

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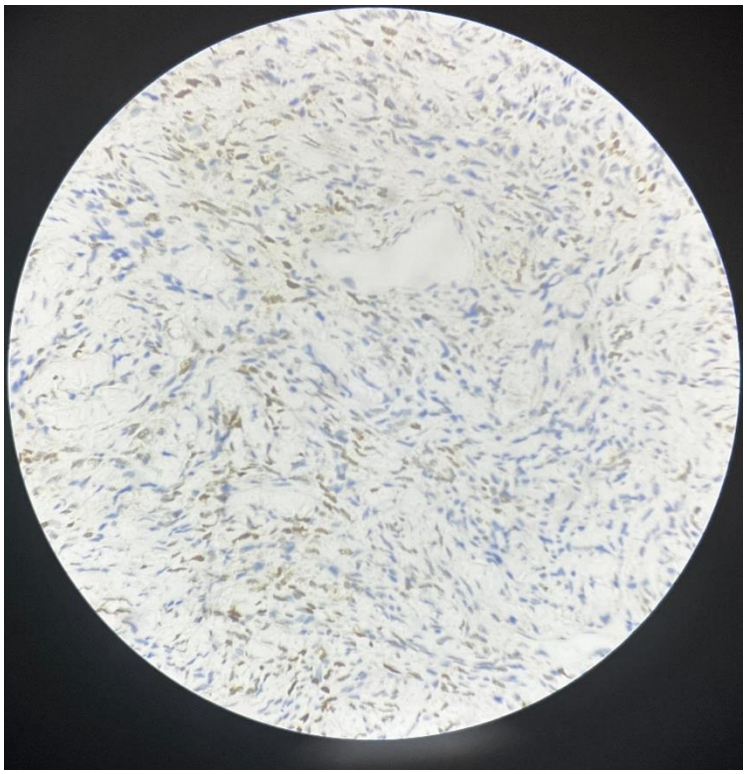

Figure 9 showing the photomicrograph of the specimen that stained positive for S-100 10X resolution. (Case II)