

Intramucosal Nevus- Case Report of a Rare Entity with Review of Literature

¹Dr. Sudeshna Bagchi, ²Dr. Swagata Gayen, ³Dr. Avishek Bhandari, ⁴Dr. Mousumi Pal

¹Post Graduate Student, Department of Oral and Maxillofacial Pathology, Guru Nanak Institute of Dental Sciences and Research, Kolkata, India

²Research Scholar, JIS University, Agarpara, Kolkata & Senior Lecturer, Department of Oral and Maxillofacial Pathology, Guru Nanak Institute of Dental Sciences and Research, Kolkata, India

³Research Scholar, JIS University, Agarpara, Kolkata & Consultant Oral Pathologist, Bardhaman, West Bengal, India

⁴Professor & HOD, Department of Oral and Maxillofacial Pathology, Guru Nanak Institute of Dental Sciences and Research, Kolkata, India

Corresponding Author: Dr. Sudeshna Bagchi, Post Graduate Student, Department of Oral and Maxillofacial Pathology, Guru Nanak Institute of Dental Sciences and Research, Kolkata, India

Type of Publication: Case Report

Conflicts of Interest: Nil

Abstract

Nevi are benign neoplasms formed by proliferation of nevus cells in skin or mucosa. Melanocytic nevus in oral cavity is quite uncommon, having an incidence of 4.35 cases per 10 million individuals. Intramucosal nevi, accounting for 55% of all intraoral nevi, are located solely in the connective tissue stroma. Compared to their cutaneous counterpart, this nevus is quite rare. We hereby present a case of intramucosal nevus in a 40 year-old female which posed a diagnostic dilemma due to its unconventionally large size and atypical colour.

Keywords: Intramucosal nevus, nevus, oral melanocytic nevus, palate

Introduction

The term *nevus*, meaning “birthmark” in Latin[1], is used to signify any malformation of the skin and mucosa that is congenital or developmental in nature.[2,3,4] However, nevus commonly refers to benign, mostly solitary and asymptomatic pigmented neoplasms, rather hamartomas, composed of nevus cells. Hence, termed more specifically

as nevocellular nevus or melanocytic nevus.[1,2,5,6,7]

Oral melanocytic nevi are classified into three types according to histology:

- (A) Junctional nevus: Lesional cells at the epithelial mesenchymal junction
- (B) Compound nevus: Lesional cells in the junctional and underlying connective tissue area; and
- (C) Intramucosal nevus: Lesional cells solely within the connective tissue.

In the intramucosal variety, proliferation of nevus cells is observed in the connective tissue which is separated from the basal layer of epithelium by a fibrous band. These, in contrast to their cutaneous counterpart, i.e. the intradermal nevus, are rarely found intraorally. [6,7,8]

They usually present as well circumscribed, asymptomatic, raised plaque of shades varying from light brown to black and are composed of nevus cells. We hereby present a case of a large intramucosal nevus of an atypical colour which was later confirmed by special stains.



Fig 1: Extraoral photograph of the patient.

Fig 2: Presence of a purplish red plaque like lesion located on left side of the hard palate and alveolar ridge with respect to extracted 26 and 27.

Case Report

A 40-year old female patient [Figure 1] from semi-urban area was referred to Dept. of Oral & Maxillofacial Pathology, GNIDSR, Kolkata with the chief complaint of an asymptomatic slow growing pigmented lesion in the palate for last 4-5 years.

Intraoral examination revealed the presence of a purplish red, round to oval (1.5 cm x 1.5 cm x 4 mm), well circumscribed, slightly raised, firm, nontender, non pulsatile and non-compressible plaque like lesion located on left side of the hard palate and alveolar ridge with respect to extracted 26 and 27. [Figure 2]

A provisional diagnosis of oral pigmented lesion was made, following which, an excisional biopsy was performed under local anesthesia and histopathologic evaluation was done.

Sections stained with H&E revealed the presence of parakeratotic stratified squamous surface epithelium backed by

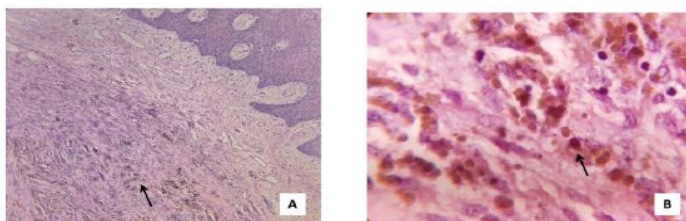


Fig 3: Sections stained with H&E revealed the presence of numerous small, ovoid nevus cells in the connective tissue

stroma (black arrow) separated by a thick fibrous band. They were organised into small round aggregates with areas of concomitant deposition of melanin. [A-4X, B-100X]

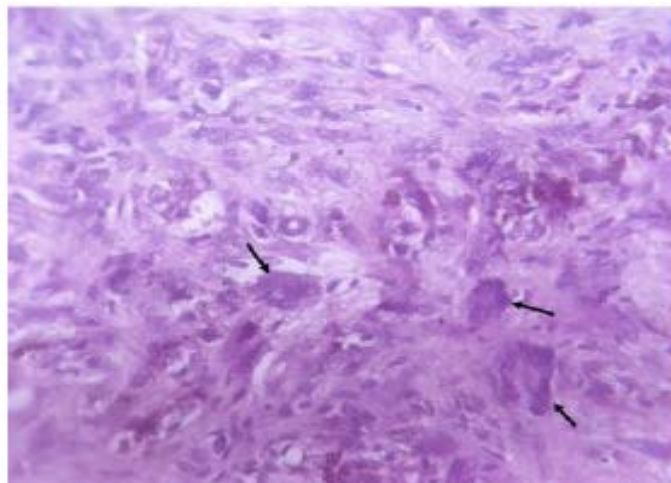


Fig 4: H&E stained section showing giant cells (40X)- black arrow

Underlying fibrovascular connective tissue. The striking feature was the presence of numerous small, ovoid nevus cells in the connective tissue stroma separated by a thick fibrous band. The cells had eosinophilic cytoplasm, uniform nuclei & indistinct cell boundaries and were organised into small round aggregates with areas of concomitant deposition of melanin. Numerous endothelial lined blood capillaries surrounding the neoplastic cells and multinucleated giant cells in close proximity to the blood vessels could also be elicited. The overall light microscopic features were suggestive of Intramucosal Nevus. [Figure 3,4,5]

Special staining with Masson-Fontana method clearly revealed the cluster of nevus cells in the connective tissue along with melanin deposition, and hence, the diagnosis of intramucosal nevus was confirmed.[Figure 6]

The excisional biopsy performed in this case was both diagnostic and curative, following which the patient showed no recurrence in the 1 year follow-up period. [Figure 7]

Discussion

Melanocytes in oral epithelium was first identified by Becker in 1927.[3] The first case of oral nevus was reported by Ackermann and Field in 1943. Initially, the term “intralamina propria nevus” was proposed by Comerford *et al.*; however, later in 1967, King *et al.* coined the term “Intramucosal nevus”. [1,3,5,7]

Nevus cells are postulated to be derived from melanoblasts, the precursors of melanocytes, or altered resident melanocytes.[1,3]

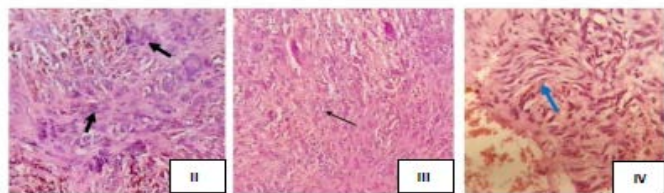
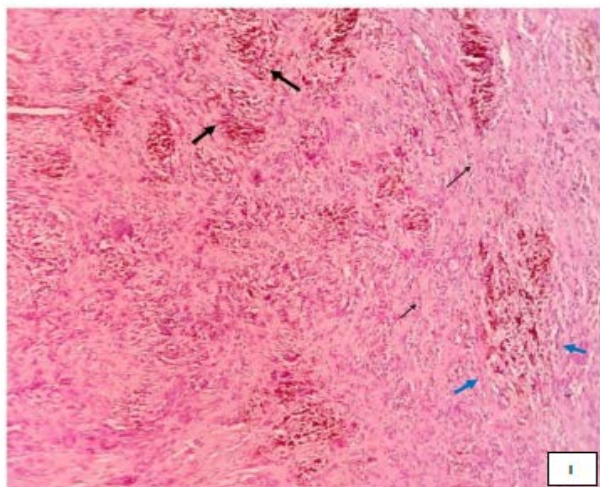


Fig 5 : I- Section stained with H&E reveals the histologic maturation of intramucosal nevus showing Type A,B,C cells.[Type A cells- Thick black arrow, Type B cells- Thin black arrow, Type C cells- Thick blue arrow] 10X

II- Type A cells- Superficial large epithelioid cells with abundant cytoplasm and increased melanin content [Thick black arrow] 40X

III- Type B cells- Uniform round-to-polygonal cells, having less cytoplasm, decreased melanin and present in intermediate portion of the lesion [Thin black arrow] 40X

IV- Type C cells- Small cells mimicking Schwann cells with spindle-shaped nuclei lacking melanin pigment and found in deeper portion of lesion [Thick blue arrow] 40X.

The pathogenesis of oral nevi is still not known; however, it is currently believed that nevi represent benign neoplasms of melanocytes, which frequently harbour oncogenic serine/threonine-protein kinase B-Raf (BRAF) or occasionally, neuroblastoma RAS viral oncogene homolog (NRAS) mutations. Oncogenic mutations probably cause the initial hyperproliferation which results in the formation of the nevi, following which a subsequent growth-arrest response with features of oncogene-induced cellular senescence results in cessation of further growth.[9,10].

Three main existing theories are there explaining the development of oral nevus. They are:

A) Abtropfung theory – The classical theory stating that nevus cells tend to drift from epidermis to dermis and proliferate.

B) Dual origin theory – Attributes to the dual origin of nevus cells. Those in the basal layer of epithelium and juxta-epithelial region of submucosa are formed from melanocytes while nevus cells deep in the dermis or submucosa originates from nerve cells, specifically Schwann cells.

C) Hochstringerung theory – This theory states that melanocytes derived from the neural crest tend to migrate upwards from the dermis to the epidermis and is reinforced by recent immunohistochemical observations. [3,6,8]

Certain histologic features of intramucosal nevus like lack of connectivity to the basal layer and the definitive band of connective tissue separating the proliferating nevus cells from the epithelium support the Hochstringerung theory more. It seems plausible that a stimuli causing proliferation lead to a mass of nevus cells in the

submucosa which migrates and pushes toward the epithelium. This being restricted causes localization of the proliferating nevus cells forming intramucosal nevus. [6] Focal pigmented lesions of oral mucosa have a prevalence of 0.83 to 5.7%.[10] Though it occurs frequently on skin, nevus in oral cavity is very uncommon. [1,7,8,10] Oral melanocytic nevus comprises 11.8% of the entire gamut of melanocytic lesions[11]; Among all types of oral pigmentation, the relative frequency of nevus was found to be 0.26% by Hassona *et al.*[10] Intraoral pigmented nevi was recorded in 0.1% of the patients in a large survey carried out by Ordie H. *et al.* [1,12] Much later, Meleti *et al.* esmitated an annual incidence of 4.35 cases per 10 million individuals.[13] They are present in people of all races, the Whites (55%) being more affected than the Black patients (23%). [5, 7]

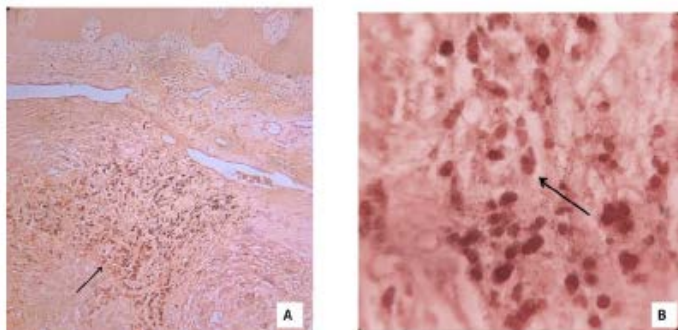


Fig 6: Section stained with Masson Fontana stain reveals: A-Nests of nevus cells in connective tissue stroma [4X]; B- Nevus cells with melanin pigmentation [100X].

The present case is an intramucosal nevus which, among the types of intraoral nevi, is more prevalent (55%) compared to blue nevi (32%), compound (6%) and junctional (5%) nevi.[1,3]

Generally, oral mucosal nevus has a slight female predilection with a ratio being 1.5:1 and in a study Buchner and Hansen also observed 65% cases of intramucosal nevi in females.[5,14] Incidentally, the present case is a female patient too. Intramucosal nevus is mainly diagnosed in the 3-4th decade of life[2,5,6] The

age group of 35-38 years usually presents more cases of intramucosal and blue nevi while a younger age group of 22-24 years shows more prevalence of junctional and compound nevus.[7] In the present case, the age of the patient is 40 years.

Intramucosal nevi are distributed almost equally between the hard palate and buccal mucosa (25%), 17% on the gingiva, 12% on the vermilion border of the lip, and about 9% on the labial mucosa.[7] The case under discussion shows the lesion in the palate and alveolar ridge.

Clinically, they are usually asymptomatic, well-circumscribed, round or oval, firm, slightly elevated spot/plaque (>80%) or flat (20%) lesions having a smooth surface. The size usually range from 0.1 cm to 0.6 cm, rarely larger upto 3 cm.[1,3,6,8,14]

Elevated nevi are usually lightly pigmented whereas flatter lesions are darker. As the nevus cells penetrate into the connective tissue, the pigmentation decreases.

Colour of the lesion varies from light brown to blue, bluish gray to black depending on the amount and location of melanin in the tissues. An individual lesion has a similar colour throughout.[7,8]

Intramucosal nevi may also be nonpigmented or amelanotic in 15–22% of the cases and present as sessile growth resembling fibroma or papilloma.[5,6] Thus, in the present case, most of the clinical features are in accordance to the available literature. However, the lesion was quite large in size which was remarkable; also, the puplish-red colour noted was quite atypical, thus making this case unique.

The malignant potential of oral nevi is still uncertain. As pre-existing pigmentation is present in 1/3 rd of melanoma patients and there are chances of misdiagnosing an early melanoma as benign melanocytic nevi; biopsy and histologic examinations of all pigmented lesions of oral

cavity are advised to obtain an accurate diagnosis.[5,14,15]

Macroscopically, nevi may proliferate in two patterns. In Unna's nevi, nevus cells grow in a papillary or nodular pattern, giving an exophytic emergence. Meischer's nevi reveal a diffuse infiltration of the cells into the sub-epithelial region giving an endophytic outlook.[3,6,16]

The narrow border between the lesion and the epithelium is referred to as the Grenz zone which is rare and found in only 16.7% of all nevi.[16] This was also noted in this particular case.



Fig 7: Post-operative photograph of the patient

Nevomelanocytes in nevi tend to remain in clusters called “theques” or occasionally cords.[3,6,7,9,16] The neoplastic cells are large, round to oval or spindle-shaped with pale cytoplasm & hydropic swollen nucleoli which occupies a large portion of the nucleus. They may contain granules of melanin pigment in their cytoplasm. The nucleus is vesicular and lacks the dendritic processes typical of melanocytes. Melanosomes are retained by nevus cells and are not transferred to adjacent keratinocytes.[1,3]

A characteristic finding, known as histologic maturation, or change in differentiation is observed in the mucosal component of intramucosal nevi which reveals:

Type A nevus cells (epithelioid): The superficial cells which classically appear as large epithelioid, with abundant cytoplasm and increased melanin content; (II) Type B nevus cells (lymphocyte-like): These are more uniform round-to-polygonal cells, having less cytoplasm, decreased melanin and are present in intermediate portion of the lesion; (III) Type C nevus cells (spindle-shaped): Small and round cells mimicking Schwann cells or fibroblasts with spindle-shaped nuclei, lacking melanin pigment and found in deeper portion of lesion. It has been observed that type A cells are more abundant than Type B cells. Thus, the highly differentiated melanocytes lose their melanocytic expression in the process of maturation and express the more embryological stable neurological differentiation in the depths of the lesion.[3,6,16]

Pseudo-inclusions in the nuclei of nevus cells as well as adipocytes in the lesion can also be found. [16] Multinucleated giant cells can be observed in 50% of the cases according to Nakajima et al.[16] Mitotic figures are rare.[6,7,16]

The histologic features in the case under discussion are thus fairly corroborative to available records. Furthermore, the type A,B,C cells can be clearly identified in the H&E stained sections as shown in Figure 5. However, no pseudo-inclusion, adipocyte or mitotic figure could be detected.

Immunohistochemical analysis with markers like S100, Melan-A, Microphthalmia Transcription Factor (MITF), c-Kit, HMB-45 also help to delineate the pattern and type of cells in the nevi.[6,16] No such difference of proliferative activity can be observed between the basal epithelial layer of the intramucosal nevi (5.5%) and that of healthy tissue (6.8%) with Ki-67.[16] However, IHC analysis of the case discussed here could not be performed due to financial constraints of the patient.

In this present case special staining by Masson-Fontana method clearly delineated the nevus cells containing melanin from its surroundings. The melanin reduces ammoniacal silver to insoluble black precipitate of metallic silver which enables light microscopy identification.[17]

Diagnosis of pigmented lesions of the oral cavity is challenging. Thus, thorough history and clinical presentations may aid in establishing an accurate diagnosis.

The differential diagnoses of intramucosal nevi include pigmented lesions secondary to endogenous and exogenous causes like melanotic macule, amalgam tattoo, hemangioma or other vascular anomalies, melanoacanthoma and melanoma.[1,3,5,12]

Melanotic macules and amalgam tattoos are usually flat whereas most of the nevi are elevated.[5] Vascular lesions are usually more purple or blue and blanch on compression whereas melanocytic proliferations do not. Malignant melanoma on the other hand is frequently associated with diffuse areas of pigmentation, ulceration, nodularity, diversity in color, and an irregular outline. Long-persisting lesion without much change in size favors pigmented nevus over melanoacanthoma and melanoma.[1,5,12]

Although malignant transformation of oral nevi is highly improbable, the most reliable approach to treatment is complete surgical excision with 2mm of safety margin.[2,3] This will also prevent the lesion from getting constantly traumatized by eating, toothbrushing.[7,12] Post-surgical reports reveal that prognosis of oral melanocytic nevi is excellent.[5] In this instance, the excisional biopsy performed was also therapeutic and the patient responded well.

Though studies have revealed malignant potential of cutaneous nevi, it is still uncertain in case of oral

melanocytic nevi.[4,14] In 2007, Meleti et al. observed that there was no association of melanoma with oral melanocytic nevi despite the predominance of both the lesions in the palate.[13] Nevertheless, diligent follow-up after treatment is recommended.[6] No recurrence was noted in the present case as well after a period of 1 year.

Conclusion

Careful diagnostic approach by clinicians helps in accurate detection of intraoral pigmented lesions, on attaining which, proper treatment can be instituted. Occasionally, early melanoma can be misdiagnosed as nevi. Thus, for all nevi including intramucosal ones, excisional biopsy is recommended which is both diagnostic and remedial. Special stains and immunohistochemistry can also be used for further confirmation. Although, no record of malignant transformation has been found till date, stringent follow-up is always advised.

Acknowledgement

We gratefully acknowledge the contributions made by Professor (Dr.) R. R. Paul, Deputy Director cum-in-charge, Research and Development, Guru Nanak Institute of Dental Sciences and Research (GNIDSR), Kolkata, Professor (Dr.) S. Kundu and Professor (Dr.) S.A. Mahmud, Department of Oral and Maxillofacial Pathology, GNIDSR, Kolkata, for their valuable guidance and support in every step. Words are inadequate to express our gratitude towards Dr. R. P. Chatterjee (Reader), Dr. N. Shah (Reader) and Dr. S. Das (Senior Lecturer) for providing their insight and expertise. Our sincere thanks to all the technical staff without whose constant assistance and technical inputs it would not have been possible to complete our work.

References

1. Kumar VR. Pigmented intramucosal nevus of gingiva: a case report. International Journal of Contemporary Dentistry. 2010 Sep 19;1(1).
2. Freitas DA, Bonan PR, Sousa AA, Pereira MM, Oliveira SM, Jones KM. Intramucosal Nevus in the Oral Cavity. J Contemp Dent Pract 2015;16(1):74-76.
3. Bashamalla R, Rao GV, Ramulu S, Sravya T. Pigmented intramucosal nevus of gingiva with a special insight on its pathophysiology: Report of a rare entity. J NTR Univ Health Sci 2017;6:181-4. DOI: 10.4103/2277-8632.215529
4. Neville BW, Damm DD, Allen CM, et al. *Oral and maxillofacial pathology*. 3rd. St. Louis: Saunders, 2009:382-384
5. Nagarajan J, Raghuram S, Bandalore SR, Patil S. Intramucosal nevus as a lesion on the lip: A case report. J Indian Acad Oral Med Radiol 2016;28:48-51. DOI: 10.4103/0972-1363.189983
6. Dutta D, Kamath VV, Rajkumar K. Oral melanocytic nevi: Report of two cases with immunohistochemical elaboration of their probable origin and maturation. Indian J Dermatopathol Diagn Dermatol 2015;2:29-33. DOI: 10.4103/2349-6029.173413
7. Rajendran R, Sivapathasundharam B. *Shafer's textbook of oral pathology*. 7th edn New Delhi: Elsevier, a division of Reed Elsevier India Pvt. Ltd, 2012:84-87
8. Jain A, Shetty DC, Rathore AS, Kumar K, Juneja S. Non-pigmented intra mucosal nevi in a young female patient: A rare case report. J Med Radiol Pathol Surg 2015;1:18-21. DOI: 10.15713/ins.jmrps.17
9. Gondak RO, da Silva-Jorge R, Jorge J, Lopes MA, Vargas PA. Oral pigmented lesions: Clinicopathologic features and review of the literature. Med Oral Patol Oral Cir Bucal. 2012 Nov 1;17 (6):e919-24. DOI:10.4317/medoral.17679
10. Hassona Y, Sawair F, Al-karadsheh O, Scully C. Prevalence and clinical features of pigmented oral lesions. International journal of dermatology. 2016 Sep;55(9):1005-13. DOI: 10.1111/ijd.13133.
11. Buchner A, Merrell PW, Carpenter WM. Relative frequency of solitary melanocytic lesions of the oral mucosa. J Oral Pathol Med 2004; 34:550-557 DOI:10.1111/j.1600-0714.2004.00238.x
12. Beena VT, Chauhan I, Heera R, Rajeev R. Oral melanotic nevi: A case report and review of literature. Oral Maxillofac Pathol J. 2010 Jan 1;1:976-1225.
13. Meleti M, Mooi WJ, Casparie MK, et al. Melanocytic nevi of the oral mucosa – no evidence of increased risk for oral malignant melanoma: an analysis of 119 cases. Oral Oncol 2007; 43: 976-981. DOI: 10.1016/j.oraloncology.2006.11.013
14. Buchner A, Hansen L S. Pigmented nevi of the oral mucosa: A clinicopathologic study of 36 new cases and review of 155 cases from the literature. Part I: A clinicopathologic study of 36 new cases. Oral Surg. Oral Med. Oral Pathol. 1987; 63; 566-572 DOI:10.1016/0030-4220(87)90229-5
15. Kauzman A, Pavone M, Blanas N, Bradley G. Pigmented lesions of the oral cavity: Review, differential diagnosis and case presentations. J Can Dent Assoc 2004;70:682-3. PMID:15530266
16. Nakajima T, Kuyama K, Sun Y. Histopathological and Immunological studies of Intramucosal nevus in the oral mucosa: With special reference to "Maturation" and "Origin" of the Nevus Cells. Int J Oral Med Sci 2010;9:88-95.
17. Bancroft JD, Gamble M. 2008. Theory and practice of histological techniques. 6th ed. London: Churchill Livingstone.