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Review

A Case Series on Intraoral Blue Nevi with a Literature Review-Based Clinico-Pathologic Comparison of Intraoral Blue Nevi with Other Oral Melanocytic Nevi

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Abstract: Nevi are pigmented lesions of bluish-black colour that may occasionally occur in the oral cavity. Out of several oral melanocytic nevi (OMN), blue nevi are significant as some variants are diagnostically challenging due to histopathological overlap with malignant melanoma. The aim of the present report was to present the clinico-pathologic characteristics of 8 new cases of intraoral common blue nevi and 22 OMN. A literature review-based comparison of the clinico-pathological characteristics of intraoral blue nevi with intramucosal nevi is presented. Analysis of the clinico-pathologic characteristics of eight common blue nevi revealed that they are generally small lesions of less than 1 cm in size and are of bluish-black colouration. These lesions were commonly identified in adults (88%), with a female predilection. The hard palate was the most common site of occurrence. These findings could be collaborated with the findings observed in the literature review. It was also revealed that a common blue nevus was the second most common lesion among all OMN. The intraoral common blue nevi included in the present series did not show recurrences or undergo malignant transformation after being followed up for up to 15 years. Unlike a common blue nevus, the literature reveals that a cellular blue nevus or its atypical variant is more diagnostically challenging, while a diagnosis of an epithelioid blue nevus should be followed up with investigations to exclude Carney complex. In conclusion, this case series and literature review reveal that OMN, including intraoral common blue nevi, are small indolent lesions with extremely low malignant transformation potential. A significantly smaller size, well-defined margins and lack of variegations in colour are all features that could be used as clues to differentiate intraoral common blue nevi from mucosal malignant melanoma. However, the diagnosis needs to be confirmed with histopathology.

Keywords: oral mucosa; oral pigmentation; nevus; blue nevus; diagnosis; histopathology

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1. Introduction

The term 'blue nevus', which was originally introduced to the literature in 1906 by Tie'che, describes dark blue lesions of the skin and currently encompasses a group of both benign and malignant lesions composed of spindle and dendritic melanocytes [1,2]. Benign blue nevi include the common, cellular, atypical, epithelioid and deep-penetrating variants, while the malignant counterpart is referred to as 'blue nevus-like melanoma' or the so-called malignant blue nevus [1]. The term cellular blue nevus was introduced by Allen in 1949 [3]. When features of both a common blue nevus and cellular blue nevus occur in a single lesion, it is recommended to assign the name of the predominant histopathological presentation [1].

Although the majority of blue nevi are solitary in presentation, multiple lesions could be associated with LAMB syndrome (lentigines, atrial and mucocutaneous myxomas and multiple blue nevi), NAME syndrome (blue nevi, atrial myxomas, myxoid neurofibromas

and ephelides) or Carney complex (myxomas, endocrine overactivity, spotty skin pigmentation and psammomatous melanotic schwannomas) [1,4–8]. Blue nevi are predominantly cutaneous lesions, although they may show a propensity to affect mucosal sites including the oral cavity [1]. Different types of cutaneous blue nevi show demographic differences. Examples are the common/dendritic blue nevus (DBN) frequently occurring in the head and neck and extremities of young adults; the scalp and buttock region of adult females commonly being affected by the cellular blue nevus (CBN); the buttocks and sacral region of young or middle-aged adults commonly affected by the atypical blue nevus (ABN) and epithelioid blue nevus (EBN) predominantly affecting young adults in the presence of Carney complex [1,6].

Oral melanocytic nevi (OMN) are benign tumours originating from neural crest or nevus cells [9–18]. The prevalence of OMN is unknown but could be considered a rare occurrence [11]. In support of this observation, in a series by Buchner et al. [14], OMN have been reported to account for 0.1% of lesions out of 90,000 biopsies received at an oral and maxillofacial unit during a period of 19 years. From the same study, it is reported that OMN may occur in both adults and children with a reported age distribution of 3–85 years, with no variations in distribution among different races detected [11,14]. Different types of OMN include junctional, intra mucosal and compound nevi; blue nevi; combined nevi; Spitz nevi; dysplastic nevi and congenital nevi [9–18]. According to the literature, the morphogenesis of junctional, intra mucosal and compound nevi is described in three phases, namely (1) proliferation of benign neoplastic melanocytes along the submucosal-mucosal junction which gives rise to a junctional nevus, (2) migration of neoplastic cells to underlying mesenchymal tissues developing into a compound nevus and (3) loss of junctional component restricting neoplastic cells in the subepithelial compartment resulting in intramucosal/subepithelial nevi [11]. The majority of OMN of the oral mucosa are believed to be acquired.

A diagnosis of OMN is generally preceded by a variety of clinical diagnoses of lesions including melanotic macules, amalgam tattoos, vascular lesions such as hemangioma and, rarely, malignant melanoma. The majority of OMN are indolent lesions. However, the fact that these OMN may clinically and histopathologically mimic malignant melanoma makes it an important group of lesions to be aware of as clinicians and pathologists. There is controversy regarding whether OMN are capable of acting as precursors for oral malignant melanoma, with Buchner et al. [14] indicating that it is a well-known fact that melanomas may occur de novo or in pre-existing nevi such as junctional nevi, dysplastic nevi and congenital nevi. In contrast, Meleti et al. [11], after following up 119 OMN for more than 8 years, have shown that none of the OMN developed into melanoma.

In contrast to OMN, with respect to cutaneous blue nevi, especially a CBN and ABN may act as precursor lesions of melanoma and may also get misdiagnosed as malignant melanoma due to overlapping histopathological features [1]. It is unknown whether the intraoral counterparts of a CBN and ABN are also precursor lesions of melanoma. However, it is important to be aware that the correct diagnosis with respect to intraoral blue nevi, irrespective of the site of occurrence or the subtype, ultimately contributes to better patient management.

Therefore, the aim of the present report was to present the clinico-pathologic characteristics of 8 new cases of intraoral blue nevi and 22 OMN. A literature review-based comparison of clinico-pathological characteristics of intraoral blue nevi with intra mucosal nevi will also be presented. The significance of the report is to create awareness among health professionals so that misdiagnosis resulting in over or under treatment of OMN is minimized. In addition, although none of the new cases reported in the present study are from syndromic patients, the criteria that preclude syndromic diagnoses are highlighted with the available literature.

2. Materials and Method

2.1. Acquisition of New Cases of OMN including Blue Nevi

The cases used in the present study are acquired from two sources. The previously unpublished case series of 8 common/dendritic blue nevi (DBN) and 22 cases of OMN were obtained from archives of the Laboratory of Oral and Maxillofacial Pathology, the Unit of Oral Medicine & Oral Maxillofacial Pathology, University of Geneva, Geneva, Switzerland, and the Department of Oral Pathology, Faculty of Dental Sciences, University of Peradeniya, Sri Lanka, respectively. Details such as age at diagnosis and gender of the patient, site of occurrence, size, whether single or multiple and outcome with respect to recurrences were recorded for each case. Thereafter, diagnoses were confirmed by evaluating existing microscopic specimens. New sections were prepared and stained with Hematoxylin and Eosin (HE) and evaluated for diagnostic accuracy when existing slides were found to be faded.

2.2. Literature Review

A literature review was performed to identify the publications that describe the clinico-pathologic characteristics of OMN and blue nevi. The terms blue nevi, oral melanocytic nevi, intraoral nevi and oral mucosal nevi were searched using Pubmed, Pubmed Central and Google scholar. These searchers revealed a total of 435 publications. Thereafter, out of the nine studies that published clinico-pathologic characteristics [9–18], five studies [9,11,13,15,16] were selected for the comparison, which included one study [13] out of multiple studies published from a single institution [10,12,14]. Case series of OMN without relevant histopathological characteristics were also excluded [17–19] in addition to case reports [20–27] (Figure 1). A literature review-based clinico-pathologic comparison of DBN and intramucosal nevi was presented using statistical analysis with a Chi-square test considering $p < 0.05$ as significant.

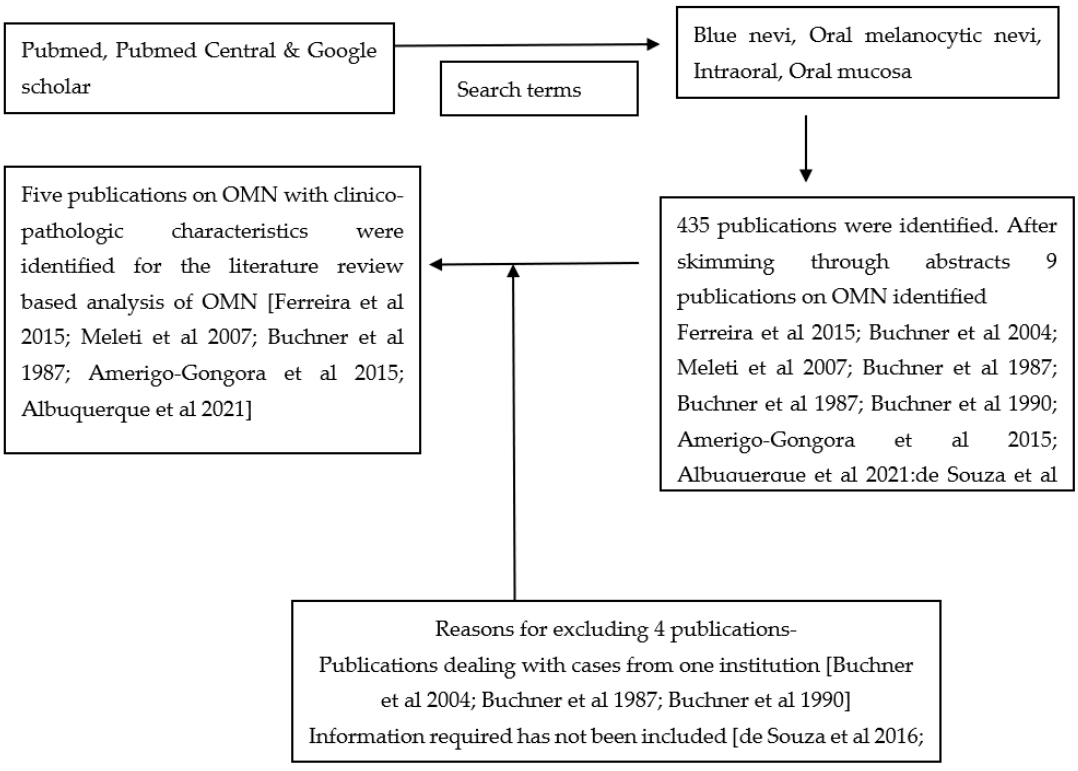


Figure 1. Criteria used for selection of the literature on OMN [9–18].

3. Results

Clinico-Pathologic Characteristics of New Case Series of Intraoral Common Blue Nevi

Table 1 shows the clinico-pathologic characteristics of eight new cases of intraoral blue nevi. Accordingly, the mean age at diagnosis was 32.3 years within an age range of 19–52 years. In the present series, intraoral common blue nevi predominantly affected females, with a male to female ratio of 1:4. All lesions detected were single lesions amounting to less than 1 cm in size, while all lesions were identified on the palate (Figure 2). No raised swelling was observed in any of the lesions, although Figure 2 shows that the blue nevus is present with inflamed minor salivary gland duct openings in the background, which may have indirectly contributed to the slightly raised presentation. The colour of the lesions varied from blue to black. All nevi included in the present series were single lesions that did not present with recurrences or undergo a malignant transformation after being followed up for a minimum of 4 years and up to 15 years (Table 1). In the present series, the majority of the lesions were clinically identified as nevi (6/8), with a single lesion each carrying a clinical impression of an amalgam tattoo and melanotic macule.

Table 1. Clinico-pathologic characteristics of intraoral common blue nevi.

No.	Age	Sex	Location	Clinical Presentation	Size	Gross	Recurrence /Follow-Up
1	52	Male	Palate, left side distal 25	Blackish-grey patch	-	0.6 × 0.4 × 0.5 cm	No/15 years
2	26	Female	Palate, median	-	-	0.6 × 0.4 × 0.1 cm	No/13 years
3	44	Female	Palate, right side facing 17–18	Blackish patch	4 × 2 mm	0.8 × 0.6 × 0.2 cm	No/11 years
4	25	Female	Palate, ant., right side	Blackish patch	2 mm	0.6 × 0.3 × 0.1 cm	No/11 years
5	19	Female	Palate, left side, facing 25	-	-	0.6 × 0.5 × 0.2 cm	No/5 years
6	39	Female	Palate, post, right side	Black patch	5 × 1 mm	0.5 × 0.3 × 0.2 cm	No/4 years
7	22	Male	Palate, left side	Bluish patch	4 × 3 mm	0.6 × 0.6 × 0.2 cm	-
8	32	Female	Palate	Bluish patch	3 × 4 mm	0.5 × 0.6 cm	No/8 years

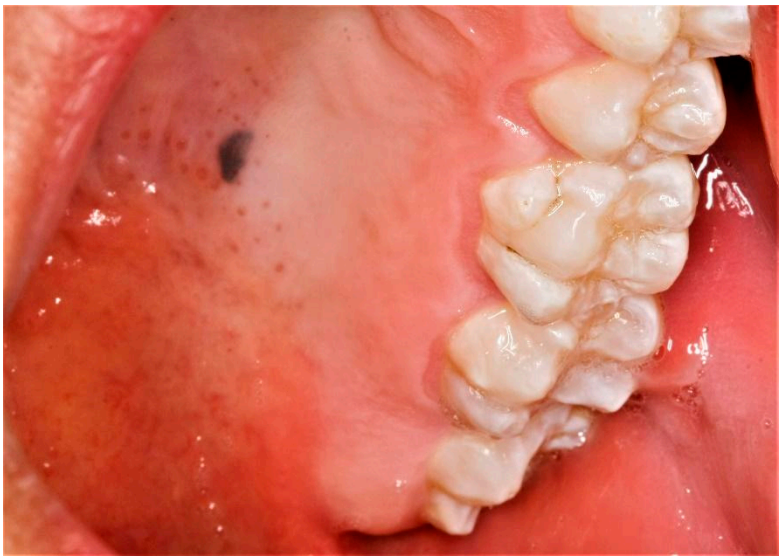
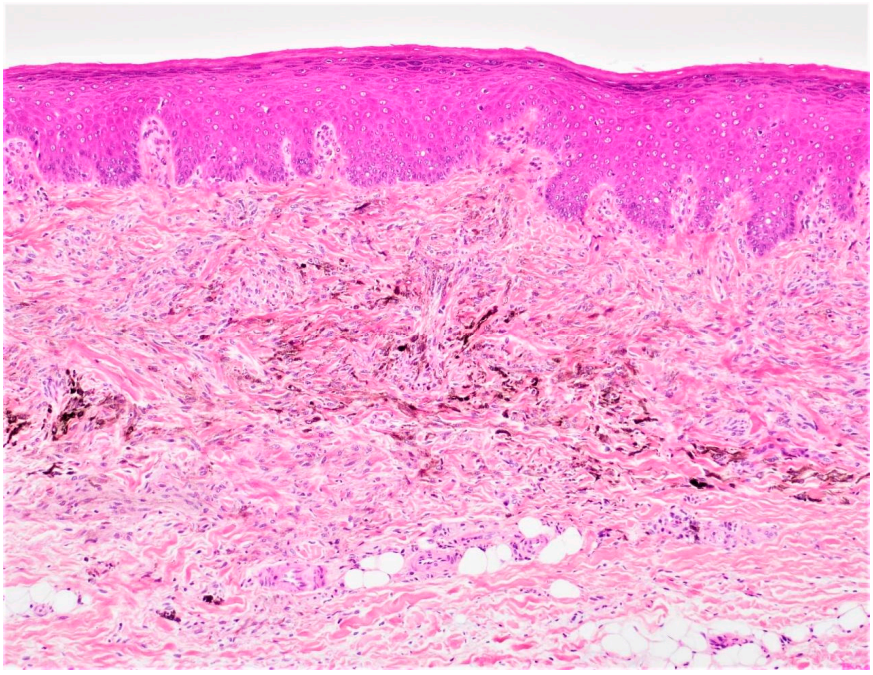
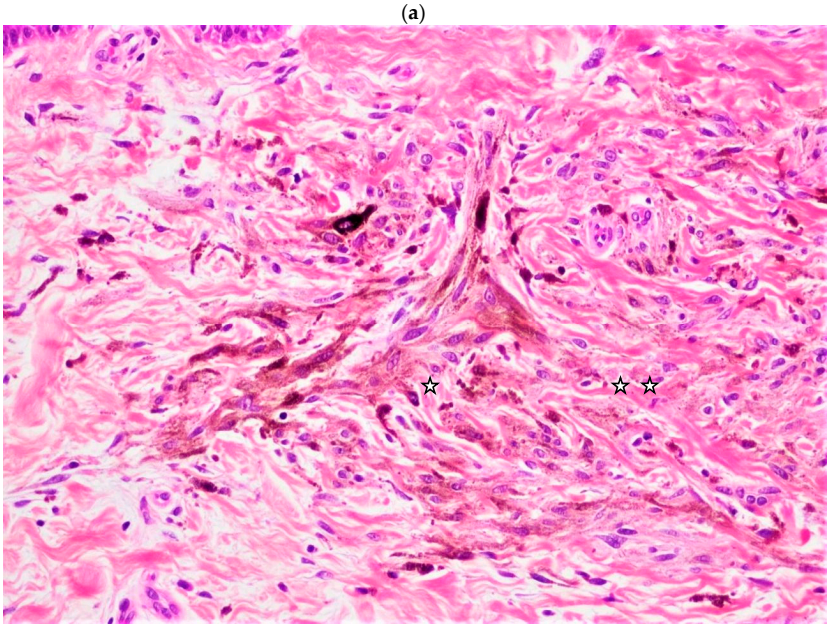


Figure 2. Clinical presentation of a palatal common blue nevus present on the palate. Note: the inflamed minor salivary duct openings on the background of the lesion are reminiscent of smoker's keratosis.

Microscopically, all lesions showed a submucosal proliferation of elongated spindle-shaped cells, with the majority of the cells containing melanin pigment within the cytoplasm (Figure 3a,b). All lesions contained varying amounts of melanophages. No cellular atypia or mitotic activity was noted. None of the DBN reported in this series was amelanotic in presentation or was evident in a background of densely sclerosed stroma. The melanocytic origin of the cells was confirmed with immunohistochemical investigations with an S-100 antibody (Figure 4a,b).

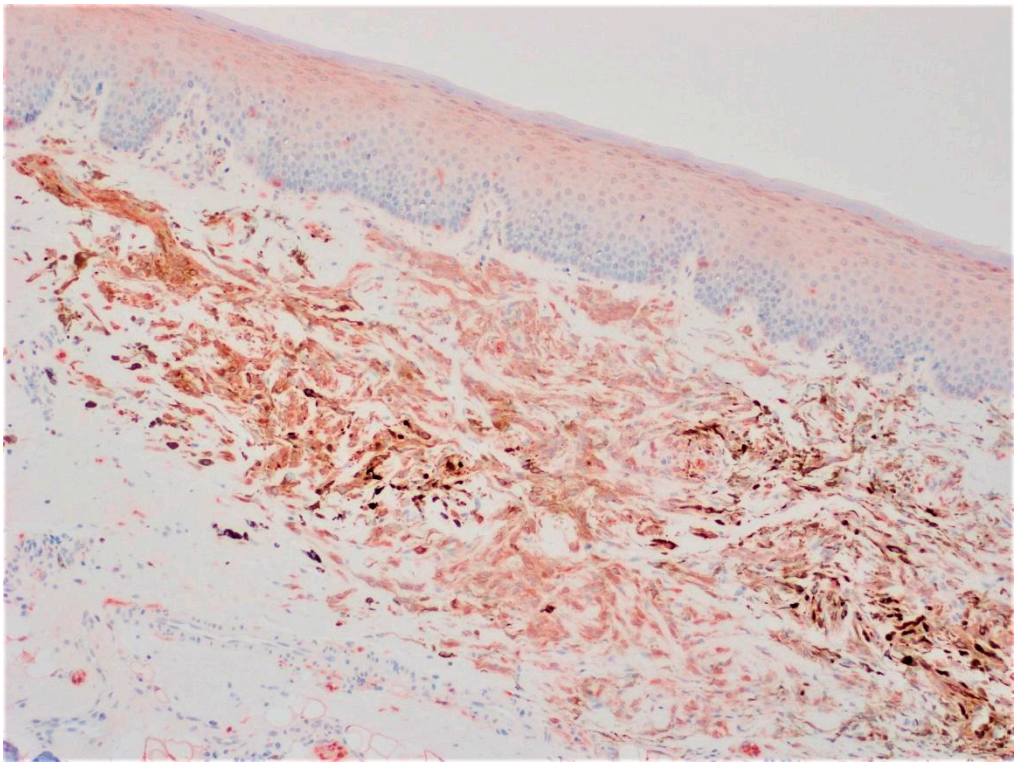


(**a**)



(**b**)

Figure 3. (**a**) Photomicrograph exhibiting pigmented dendritic nevus cells in the submucosa (HE) ×10. (**b**) Photomicrograph exhibiting pigmented dendritic nevus cells in the submucosa (HE) ×40. A few nevus cells are highlighted in (**b**) with five pointed stars.



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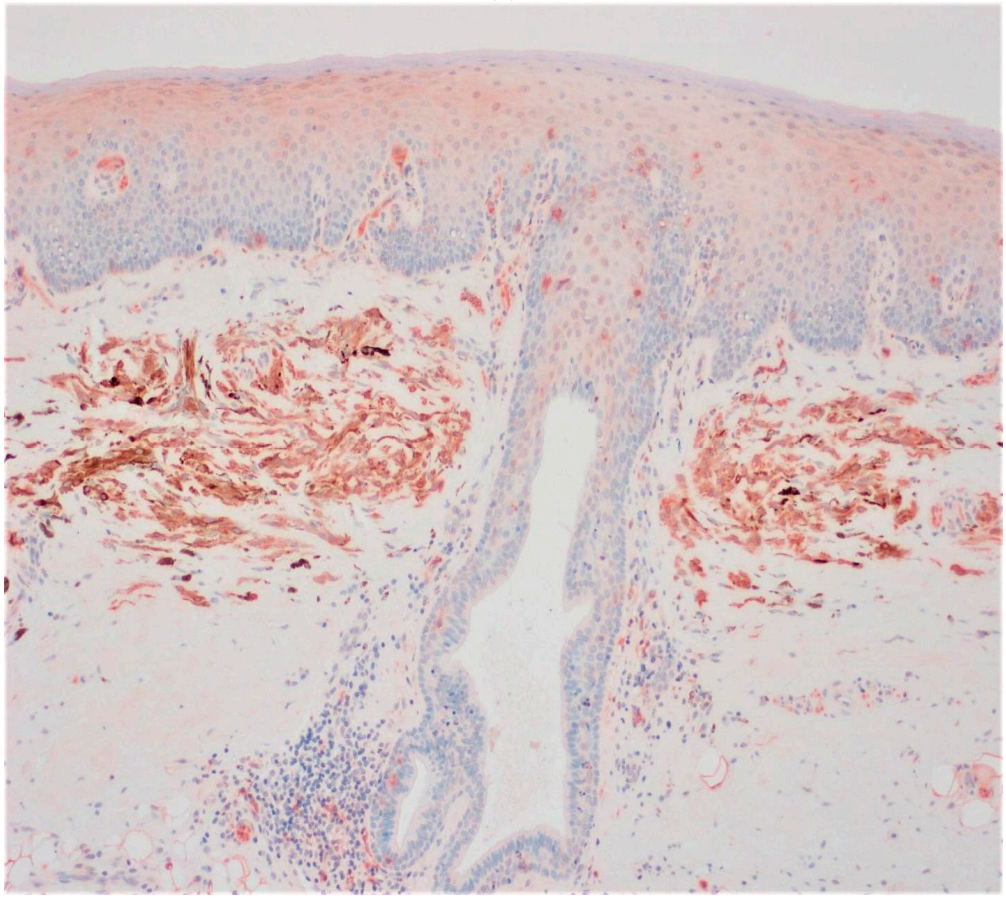

(**b**)

Figure 4. (**a**,**b**) Immunohistochemically stained section to show the origin of the nevus cells (S-100) ×10; 40. Note: all S-100-positive nevus cells are stained in a golden brown colour.

Table 2 shows the distribution of OMN reported in five published studies and the present study. Out of the 521 OMN reported, the common blue nevi accounted for 25.7% (134/521) of the cases reported and were the second most common lesions reported in all case series [9–16]. The most common lesions among OMN were submucosal/intramucosal nevi, which accounted for 61.5% (315/512) of the cases. The literature review-based clinico-pathologic comparison was performed with DBN and intramucosal nevi as the remaining nevi were not observed in considerable amounts for meaningful statistical comparison. Accordingly, when considering both intramucosal and intraoral DBN, both may occur at any age, although the majority have been shown to occur in adults. In elderly patients, DBN are more common (32%) compared to intramucosal nevi (20%). Both lesions show a female predilection; however, a lack of relevant information in some references regarding gender distribution precludes definitive conclusions [9,16]. With respect to the site of occurrence, the most significant observation is the fact that DBN show a predilection to occurring at the hard palate compared to other mucosal sites. On the other hand, intramucosal nevi do not show an overwhelming predilection to the hard palate and may occur in all mucosal sites including in keratinized and non-keratinized mucosal surfaces (Table 3).

Table 2. Literature review-based subtypes of OMN from a series of cases published to date.

Article (Total Number of Cases) [Reference]	Intramucosal Nevi	Junctional Nevi	Compound Nevi	DBN	CBN	ABN	EBN	Dysplastic Nevi	Spitz Nevi	Combined
Buchner et al. (191) [13]	105	10	12	61	0	0	0	0	0	03
Meleti et al. (119) [11]	96	05	07	10	0	0	0	0	0	01
Ferreira et al. (100) [9]	61	03	07	23	02	0	0	02	0	02
Amérigo-Góngora M et al. (10) [15]	04	01	02	03	0	0	0	0	0	0
Albuquerque DM et al. (71) [16]	30	03	09	29	0	0	0	0	0	0
Jayasooriya et al. (30) present study	19	0	03	08	0	0	0	0	0	0

DBN—dendritic blue nevus (dendritic (common) blue nevus); CBN—cellular blue nevus; ABN—atypical blue nevus.

Table 3. Literature review-based comparison of clinico-pathological characteristics of intramucosal nevi compared with common blue nevi.

Feature	Intramucosal Nevi (n = 282) (%)	Common Blue Nevi (n = 128) (%)	X^2 Test
Age in years			
<20	20 (7.1)	15 (11.7)	$p = 0.007$
21–50	203 (72)	72 (56.2)	
>51	59 (20.9)	41 (32.1)	
Gender			
Male	82 (31.8)	47 (44.8)	$p = 0.019$
Female	176 (68.2)	58 (55.2)	
* Unknown	24	23	
Site			
Hard palate	88 (31.4)	85 (68.0)	$p = 0.000$
Gingiva	63 (22.5)	02 (1.6)	
Buccal mucosa	59 (21.1)	16 (12.8)	
Vermillion border/labial mucosa	70 (25.0)	22 (17.6)	
Other	02	03	

Based on [9,11,13,16] and the present series. * Gender distribution is not given in [9]; wrong numbers related to gender are available in the table given in [16] and were excluded from the analysis.

The literature review also revealed information on the size of the lesions, with the majority of the lesions, including the present series, providing evidence that more than 95% of the OMN, including the DBN, are smaller than 1 cm in their greatest dimension (Table 1) [9,13,14]. There is evidence to show that epithelioid, cellular and atypical blue nevi may also rarely occur in the oral cavity [9,28–35].

4. Discussion

4.1. How Do We Clinically Differentiate Nevi from Melanoma?

It is the observation of the present authors that patients get alarmed when they encounter nevi, which resemble melanoma due to similarities in the colour of the lesions; namely, both have a bluish-black colour [36]. Nevi may also make the patients invariably think of melanoma that behaves aggressively, especially mucosal melanoma. From a scientific viewpoint, some nevi such as cutaneous cellular and atypical cellular blue nevi are significant as they may clinically and histopathologically resemble melanoma in addition to being a precursor to the development of cutaneous melanoma [1]. The ABCD rule, which assesses 'asymmetry, borders, colour and diameter' in the clinical diagnosis of melanoma, has been validated for skin lesions [36]. However, it is not clear whether this same principle could be applied to intraoral lesions as well. Therefore, the present study is conducted to present the clinico-pathological characteristics of OMN, including intraoral blue nevi, to reiterate the indolent nature of the lesions. In contrast to OMN, oral mucosal melanoma comprises aggressive lesions with an extremely poor outcome [37–44].

The literature review and the present series reveal that DBN or common blue nevi are indolent lesions that appear as single, smooth, sharply circumscribed and round-to-oval lesions that generally do not exceed more than 1 cm in their greatest diameter [9–16]. However, it is also important to keep in mind that the large size should not preclude a diagnosis of DBN, as a case report describes an intraoral blue nevus that exceeded 5 cm in diameter. In addition, Ferreira et al. [9] show that only approximately 15% of the lesions included in their series of OMN exceeded more than 2.5 cm in size. Thus, by applying the ABCD rule, namely, the diameter of the lesion, it could be concluded that an overwhelming majority of OMN including intraoral blue nevi do not exceed >6 cm in diameter and could be used as a reliable clue to exclude melanoma.

When the blue nevus was first described by Tièche, he coined the term due to the blue-black colour of the lesions [2]. The Tyndall effect is generally thought to be responsible for the blue colour of the lesion, which occurs from melanocytes situated deep in the dermis or lamina propria in the mucosa. The reason for colour variations observed in the blue nevi could be attributed to the presence or absence of melanocytes in the overlying epithelium/epidermis, the depth at which melanocytes are present and the number of melanin-containing melanocytes present in the lesion [31]. Intraoral blue nevi have also shown a range of colours that vary from blue to blue-black or grey [9–16] (Table 1). However, none of the blue nevi described in reports were found to show colour variegations, which is another clue to differentiate these OMN from melanomas.

4.2. Where Do Dendritic Blue Nevi Commonly Occur in the Oral Cavity?

The literature review revealed that DBN predominantly occurred on the palate (Table 3), while all the new cases were also from the palate (Table 1). Although it is not possible to exactly give a reason for the site predilection, one reason could be the contribution of neural crest cells towards the development of the palate itself [45] and it could be postulated that remnants of neural crest cells that remain after the development of the palate give rise to nevi as well as malignant melanomas. However, the literature review also revealed that all mucosal sites including keratinized and non-keratinized mucosae could be affected by OMN, where the same theory cannot be applied.

4.3. Are Females More Prone to Developing Oral Melanocytic Nevi?

The literature review of OMN [9,11,13,14,16] and the present series of blue nevi indicates a female predilection (Tables 1 and 3). Based on the available information, it is difficult to determine whether the female predilection is artificially enhanced due to the fact that females may be more concerned and seek treatment more often compared to males, or whether the finding observed is due to a true increase in the occurrence of OMN in females compared to males.

4.4. Why Do General Dental Practitioners Need to Be Aware of Oral Melanocytic Nevi?

According to the literature, the majority of patients with OMN are unaware of the existence of such lesions [12,13], while a few lesions may present with pain and tenderness. Buchner et al. [13] also indicate that general dental practitioners (GDPs) may play a role in the identification of OMN. GDPs may easily identify lesions that are gradually enlarging, especially in patients who keep up follow-up appointments or those who regularly go for routine check-ups. In the present series, in contrast to the observation by Buchner et al. [12], all patients were aware of the lesions when they sought treatment. However, all the lesions were asymptomatic.

With respect to the lesions included in the present series, the majority were clinically diagnosed as nevi. However, in contrast, Buchner et al. [12] have reported that smaller numbers of their cases were diagnosed as malignancies including melanoma. In addition, amelanotic nevi may also carry a clinical impression of reactive lesions such as irritation fibroma and papilloma [12]. Therefore, it is important to remember that all OMN that present in patients may not carry an indolent clinical impression and, therefore, incisional biopsies of larger lesions are recommended to avoid overtreatment.

With respect to the configuration of the OMN, the majority were described as well circumscribed, flat or slightly raised lesions [9,11,13,14]. In addition, junctional or compound nevi have a higher chance of being pigmented, while intramucosal lesions could be non-pigmented [14]. The majority of non-pigmented nevi have been described to have a raised configuration. It is important to consider the configuration to narrow down the clinical differential diagnosis. For example, if the lesion is slightly raised, it can be differentiated from racial pigmentation, melanotic macules or amalgam tattoos, all of which are flat lesions. However, with the slightly raised configuration, it is important to remember the other raised lesions that should be considered in the differential diagnosis as melanoma [14].

4.5. How Do Oral Melanocytic Nevi Occur?

Information on the etiology and pathogenesis of OMN is sparse but thought to be similar to their cutaneous counterpart [11]. At present, it is confirmed that cutaneous melanocytic nevi are in fact benign neoplasms comprising melanocytes that may harbour BRAF oncogenic mutation. It is thought that the oncogenic mutation is responsible for the initial hyperproliferation that gives rise to the nevus and the subsequent growth arrest is the result of oncogene-induced cellular senescence [46]. Considering the many similarities between cutaneous and OMN, it is plausible to conclude that the same pathogenic mechanism contributes to the development of cutaneous nevi and to the development of OMN as well.

4.6. What Types Other Than Common Blue Nevi Occur in the Oral Mucosa and What Are Their Diagnostic Challenges?

The literature review revealed that cellular and atypical blue nevi may also occur in the oral mucosa, though they are significantly rarer than DBN [9,11,31,34]. Unlike DBN, cellular blue nevi and atypical cellular blue nevi may pose a diagnostic challenge to pathologists [1]. CBN are histopathologically described as a well-circumscribed nodular lesion composed of lightly pigmented melanocytes. The pigmentation observed in the lesions has been described as being due to melanophages. Mitotic activity and necrosis are two features that may result in the misdiagnosis of CBN as melanoma and, therefore, it is

worthwhile to remember to consider a diagnosis of an atypical cellular blue nevus rather than melanoma in the presence of such features. It is also recommended to consider the size of the lesion as a clue to differentiate ABN/CBN from melanoma, although there is controversy regarding the cut-off values with respect to size. It is the general rule to accept that as the size increases from 3 cm to 5 cm a diagnosis of melanoma becomes more likely than of ABN/CBN [34,47].

The blue nevus has rarely been reported to appear in a plaque form [28]. It may present as a confluent lesion or be composed of several papules that vary from 1 cm or more. As indicated previously, the significance of the plaque-type blue nevus is its cellularity. Clinicians should be aware of the lesion as it may mimic satellite metastasis of melanoma [28]. Nevus of Ota, on the other hand, has been described to occur more often in Asian females. Age at onset shows a bimodal distribution with approximately 50% appearing at birth or in early childhood and the rest during the next four decades of life. Oral involvement is rare with only five cases reported in the literature to date [28]. A comparison of a DBN, plaque-type blue nevus and nevus of Ota reveals the following differences. Size wise, a DBN is the smallest, amounting to less than 1 cm, a plaque-type blue nevus extends to several centimetres, while the nevus Ota is the largest and more than 5 cm in size. All three lesions show a female predilection and are bluish-black in colour with the exception of the nevus of Ota, which could have a brown colour in addition to a similar colour to the other two lesions. A nevus of Ota has a higher chance of developing into a malignancy, especially in Caucasians, while the other two lesions have rarely been reported to undergo malignant transformation [28].

Murali et al. [1] describe a malignant counterpart of the blue nevus. It is described as a lesion that contains collections of cytologically abnormal melanocytes and may occur in a pre-existing blue nevus, or at the site of an excised blue nevus [31]. A diagnosis of a malignant blue nevus should be excluded, especially in lesions larger than 3 cm, lesions that show a presence of a nuclear pleomorphism, atypical mitotic figures, necrosis, a destructive growth pattern and a lack of biphasic appearance [31]. Although none of the lesions described in the present series (Tables 1 and 2) showed malignant transformation, the literature review revealed a malignant transformation of a blue nevus on the upper lip, which occurred in a 50-year-old man. Therefore, it is important to be aware that in extremely rare situations, blue nevi may acquire the ability to undergo a malignant transformation [48].

An epithelioid blue nevus (EBN) is an extremely rare histologic variant of a blue nevus that could be associated with Carney Complex [1]. An EBN is characterized by two types of melanocytes, namely, large, heavily-pigmented polygonal or epithelioid-shaped melanocytes that do not show maturation towards the deep aspect of the lesion and a small number of lightly pigmented cells fusiform or spindle-shaped cells often arranged into short fascicles [32]. A lack of maturation is a significant finding that could be used to differentiate an EBN from acquired nevi; however, it is also a feature that may result in this lesion being misdiagnosed as melanoma, in addition to its mitotic activity [1,32]. To date, to the best of our knowledge, only two intraoral epithelioid blue nevi have been described, and a single patient was subsequently diagnosed with Carney complex [32]. Therefore, it is worthwhile to remember to exclude Carney complex in patients who get diagnosed with an EBN, while also remembering that an EBN may occur sporadically in patients without Carney complex as well [49,50].

4.7. How Do We Manage Oral Melanocytic Nevi?

With respect to management of a cutaneous DBN, as a clinician, it is recommended that typical lesions without any significant clinical differential diagnoses, particularly melanoma, could be left alone after reassuring the patient. On the other hand, if there is a doubt as to the definitive diagnosis, it is recommended that the patient is referred to a dermatologist. In the case of recurrent lesions in a satellite form after excision, they should be well assessed to exclude malignant transformation [1]. However, it is difficult to

determine with the existing literature whether the same management strategies could be applied to an oral DBN as well as all the cases that have been assessed in the present report which have been excised [9,11,13,14].

In conclusion, this case series and literature review reveal that OMN, including intraoral common blue nevi, are small indolent lesions, with extremely low malignant transformation potential. Significantly smaller size, well-defined margins and lack of variegations in colour are all features that could be used to differentiate an intraoral DBN from mucosal malignant melanoma.

4.8. Future Directions

It is worthwhile to explore the feasibility of validating the 'ABCD' rule to differentiate oral melanotic nevi from oral mucosal melanomas.

As the majority of the studies have been conducted as hospital-based studies, it is prudent to design a population-based study to identify the true prevalence of oral melanocytic nevi including blue nevi. A similar study would allow us to clarify whether the demographics including gender and site predilections observed in hospital-based studies are accurate.

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