

## CASE REPORT

# Oral Blue Nevus: Two case reports and literature review. Nevus azul oral: Dois relatos de caso e revisão de literatura

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## ABSTRACT

**Case Description** We report two cases of oral Blue Nevus. The first case is a 32 years old female patient with a brown-blue lesion on hard palate, with no clinical symptoms that has always been present but that recently had been growing. The second case is a 36 years old male patient with a brown macule on hard palate.

**Clinical Findings** On case report 1, oral examinations revealed an irregular brown-blue macule, measuring 13 x 6 mm on hard palate. On case report 2, oral examination showed an oval brownish macule also located on hard palate.

**Treatment and Outcome:** Excisional biopsy was performed in both cases and histopathology analyses revealed diagnosis of Blue Nevus.

**Clinical Relevance:** Diagnosis of pigmented lesions of the oral cavity can be challenging once there are a variety of causes such as racial pigmentation, systemic diseases, use of medication, metal tattooing, melanocytic nevus, melanoacanthoma, and melanoma. The correct diagnosis of this type of lesion is important to help professionals offer the best care for the patients and highlighting clinic criteria to differentiate malignant pigmented lesions is fundamental.

## KEYWORDS

Blue Nevus; pigmentation; diagnosis; oral health.

## RESUMO

**Relato de Caso:** Relatamos dois casos de Blue Nevus oral. O primeiro caso é de uma paciente de 32 anos, do sexo feminino, com lesão marrom-azulada em palato duro, sem sintomas clínicos que sempre estiveram presentes, mas que vinham crescendo recentemente. O segundo caso é de um paciente do sexo masculino, 36 anos, com mácula marrom no palato duro.

**Achados clínicos:** No relato de caso 1, os exames orais revelaram uma mácula marrom-azulada irregular, medindo 13 x 6 mm no palato duro. No caso clínico 2, o exame bucal mostrou uma mácula oval acastanhada também localizada no palato duro.

**Tratamento e Resultado:** A biópsia excisional foi realizada em ambos os casos e a análise histopatológica revelou o diagnóstico de Nevo Azul.

**Relevância clínica:** O diagnóstico de lesões pigmentadas da cavidade oral pode ser desafiador, uma vez que há uma variedade de causas, como pigmentação racial, doenças sistêmicas, uso de medicamentos, tatuagem em metal, nevo melanocítico, melanoacantoma e melanoma. O correto diagnóstico desse tipo de lesão é importante para auxiliar o profissional a oferecer o melhor atendimento aos pacientes e destacar critérios clínicos para diferenciar lesões malignas pigmentadas é fundamental.

## PALAVRAS CHAVE

Nevo Azul; pigmentação; diagnóstico; saúde bucal.

## CLINICAL RELEVANCE

This study is relevant as it reposts two cases of diagnosis and management of Blue Nevus. The correct diagnosis of this type of lesion is important to help professionals offer the best care for the patients.

## INTRODUCTION

Blue Nevus (BN) describes a heterogeneous group of skin lesions characterized by dermal proliferation of melanocytes presenting as a benign, congenital pigmented skin malformation.<sup>1,2</sup> In most of the cases, these alterations are acquired and present as a solitary lesion but may also be congenital and appear in multiple sites. This lesion typically presents as an asymptomatic blue or black-blue single macule or papule due to the pigmentation of melanocytes located in the mid-dermis.<sup>3,4</sup>

Pigmented lesions of the oral mucosa can be clinically classified as (1) diffuse or multifocal macular pigmentations, including entities such as physiological racial pigmentation, melanosis associated with systemic diseases, smoker melanosis, melanosis caused by drugs and, pigmentation by heavy metals and (2) solitary focal pigmentation, including melanotic macula, amalgam tattooing, melanocytic nevus, melanoacanthoma, and melanoma.<sup>5,6</sup>

The most common location areas are on the head and neck, sacral and extremities. Blue nevi have also been reported in extracutaneous sites as oral and sinonasal mucosa, uterine cervix, prostate, esophagus and various other locations.<sup>1,7</sup>

There are two types of BN described, common blue nevus and cellular blue nevus, which are clinically indistinguishable. The common blue nevus, the most common subtype found in the oral cavity, consists of a collection of thin, elongated bipolar, spindle-shaped melanocytes, arranged in short fascicles parallel to the overlying epithelium.<sup>8</sup> Microscopically, cellular blue nevus is distinguished by a biphasic proliferation of hypercellular, nodular aggregates of nevic cells.<sup>9</sup>

Atypical melanocytic proliferations frequently need expert consultation and it is important to conduct the treatment management based on a review of the clinical situation and on pathologist's opinions. The literature on reports and management of these lesions is scarce. There is risk of over- and undertreating patients with ambiguous melanocytic tumors because it is essentially not known which lesion is benign and which is malignant.<sup>10</sup>

Even though BN has no malignant potential, any these lesions should be excised and sent for histopathologic evaluation to rule out the possibility of melanoma.<sup>11</sup> In this study we report 2 new cases of BN on hard palate.

## CASE REPORT 1

A 32-year-old female patient presented to our Stomatology Clinic with a pigmented lesion located on hard palate. The patient reported that this lesion has always been present, but, over the last 5 months, she noticed it was enlarging.

The Patient reported to be healthy, did not use any routine medication and had no history of health problems. Extra oral examination was within normal limits.

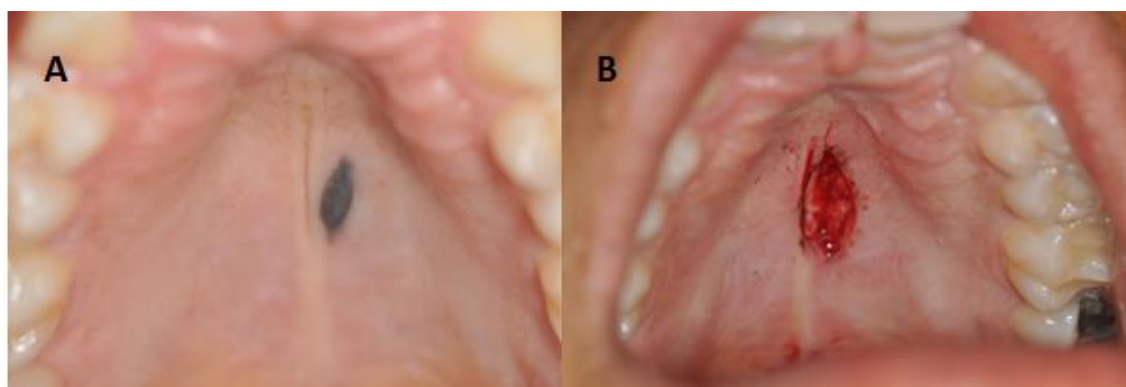
Intra oral examination revealed a brown-blue irregular, well defined macule, measuring 13 x 6 mm with no clinical symptoms, located on the left side of hard palate (Figure 1). Possible diagnoses were Melanocytic Nevus, Melanoacanthoma and Melanocytic macule. Excisional biopsy was performed and histopathology revealed squamous orthokeratinized epithelium, connective tissue exhibiting proliferation of fusiform melanocytes dispersed deeper in the tissue. The cells showed cytoplasm rich in melanosomes and the conjunctive contained melanophages (Figure 2), which led to the diagnosis of Common Blue Nevus.

## CASE REPORT 2

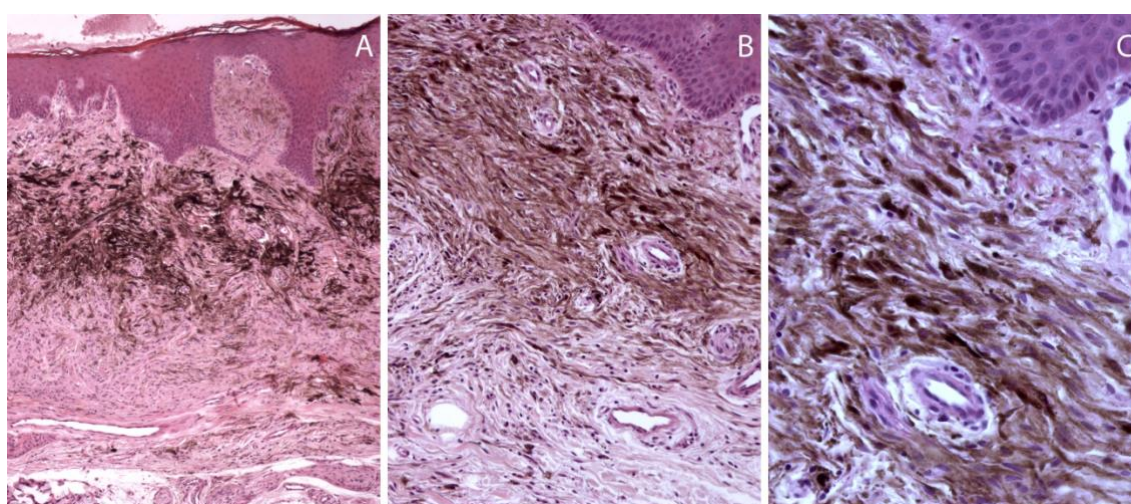
A 36-year-old male patient was referred to our clinic by his dentist presenting a dark color lesion on hard palate. The patient reported that he had never noticed this lesion before so he could not tell how long it's been present and if it's been enlarging.

The patient also reported to be healthy, did not use any routine medication and had no history of health problems either. Extra oral examination showed normality.

Intra oral examination showed an oval brownish macule with normal consistency, located on the right side of the hard palate, measuring approximately 5 x 3 mm. The possible diagnoses were Melanocytic Nevus, melanic blemish and Blue Nevus. Excisional biopsy was performed and histopathology revealed fragments of oral mucosa coated by stratified, parakeratinized squamous epithelium exhibiting hyperkeratosis and acanthosis. In the lamina propria of fibrous connective tissue, intense fusocellular proliferation was observed, among which we evidenced innumerable cells containing finely granular pigment with



**Figure 1:** A- Clinical aspect of the lesion; B- view after excisional biopsy.



**Figure 2:** Histopathological finding of the case report 1 (H&E stain). A- Note cytoplasm rich in melanosomes (10x); B- Melanocytes dispersed in conjunctive tissue (20x); C- Cytoplasm rich in melanosomes (40x).

an intracytoplasmic brownish color (Figure 3). The final diagnosis was Cellular Blue Nevus.

## DISCUSSION

Blue Nevus was first described by Tièche<sup>12</sup> in 1906, as a small, well defined, blue or blue-black spot, more common on the face and the extremities.<sup>13</sup> The blue color of the lesion is due to the Tyndall effect. The melanin particles are deep within the dermis, which causes the reflected light to pass through the tissue above and interact with particles in a colloidal suspension.<sup>2, 13</sup>

The clinical differential diagnosis included exogenous or endogenous pigmentation, intraoral melanocytic nevus, melanotic macule, and malignant melanoma.<sup>13</sup> Exogenous pigmentation is commonly due to foreign-body implantation in the oral mucosa. Endogenous pigments in-

clude melanin, hemoglobin, hemosiderin and carotene.<sup>14</sup>

The starting point for a clinical diagnosis of melanoma is the ABCD criteria, which is based on gross characteristics such as ulceration and bleeding. The ABCD determines 4 features which are asymmetry (A), border irregularity (B), color variegation (C), and diameter larger than 6 mm (D). It was developed and popularized in the mid-1980s as an aid to educate physicians and the public to identify melanoma at earlier stages.<sup>15</sup>

Hyperpigmentation of the oral mucosa, in most cases involving the hard palate, can also be caused by prolonged use of antimalarial medications, such as chloroquine diphosphate and hydroxychloroquine sulfate, that are commonly used for treatment of systemic and discoid lupus erythematosus and rheumatoid arthritis.

These drugs can stimulate melanocytes to produce melanin

**Table 1.** Most common findings reported in the literature about oral Blue Nevus. Buchner & Hansen, 1987 data from \*1968-1978, \*\*1979-1986

Reference	Gender	Age	Race	Location	Clinical aspect	Size (mm)
<b>Buchner, 1987*</b>	Female	20	Asian	Hard palate	Raised	4
	Male	29	White	Upper labial	-	2
	Female	32	-	Hard palate	Raised	1
	Male	22	White	Upper labial	Raised	-
	Female	25	White	Hard palate	Flat	-
	Female	67	White	Vermilion border	-	2
	Female	36	White	Hard palate		8
<b>Buchner, 1987**</b>	Male	40	-	Hard palate	Flat	2
	Male	62	White	Hard palate	-	3
	Male	5	Hispanic	Hard palate	Flat	20
	Male	48	White	Hard palate	Raised	3
	Female	37	-	Hard palate	Raised	4
	Male	59	White	Hard palate	Flat	2
	Male	17	White	Hard palate	-	3
	Male	42	Hispanic	Hard palate	-	2
	Male	73	Asian	Soft palate	-	7
	Male	57	Asian	Hard palate	Flat	4
Female	47	Black	Hard palate	Raised	-	
<b>Buchner, 1987</b>	9 Male	0-9 1	4 White	10 Hard palate	3 Raised	1-3 6
	2 Female	10-19 1	1 Black	1 Soft palate	4 Flat	4-6 2
		30-39 1	2 Asian			7-9 1
		40-49 4	2 Hispanic			>13 1
		50-59 2				
		60-69 1				
		70-79 1				
<b>Barker GR, Sloan P, 1988</b>	Male	53	White	From lower incisors to the anterior floor of the mouth	Just swelling	15x10
<b>Pinto, 2003</b>	Male	58	-	Oral mucosa	dark blue, firm, sessile mass	4x3
<b>Fistarol, 2005</b>	Female	20	-	Buccal mucosa	Slightly elevated	30x35
<b>M. Amerigo-Gongora et al., 2017</b>	Male	50		Palate	Raised	3
	Female	47		Palate	Flat	4
	Male	31		Oral mucosa	Raised	7
<b>Pennacchiotti G, Oviedo C, Ortega-Pinto, 2018</b>	Male	6	Hispanic	Mandibular gingiva	Flat, blurred limit, dark brown	8

which causes hemosiderin deposition, possibly facilitating focal microscopic hemorrhage. The exact mechanisms involved in this type of hyperpigmentation are not yet well established and these alterations are generally reversible a few months after the use of the medication is interrupted.<sup>16-17</sup>

Oral pigmentation can vary in color depending on quantity and depth or location of the lesion. Superficial lesions are generally brown, while those deeper are black or blue. Melanin is produced by melanocytes and is also synthesized by nevus cells which derive from the neural crest and are found in the skin and mucosa. The clinical history, uniformity and regularity of the lesion are very important in determining the clinical differential diagnosis.<sup>8</sup> Melanocytic nevi are more common on the skin than on the oral mucosa. Clinically, oral nevi are small, well circumscribed macules but commonly appear as slightly raised papules of brown, bluish-gray, or almost black color and occasionally nonpigmented. Etiology and pathogenesis can be related to cutaneous lesions and constitute benign neoplasms of cutaneous melanocytes, which frequently harbour oncogenic serine/threonine-protein kinase B-Raf (BRAF) or, less commonly, neuroblastoma RAS viral oncogene homolog (NRAS) mutations.<sup>8,18,19</sup> Oral melanoma is rare and represents less than 1% of all oral malignancies. It is characterized by proliferation of malignant melanocytes along the junction between the epithelial and connective tissues, as well as within the connective tissue. It is more commonly found in hard palate and gingiva. Clinically, oral melanoma may present as an asymptomatic, slow-growing brown or black patch with asymmetric and irregular borders or as a rapidly enlarging mass associated with ulceration, bleeding, pain and bone destruction. In approximately one-third of the cases, oral melanomas are characterized by a prolonged radial growth phase followed by a vertical growth phase; whereas others exhibit a faster progression into a vertical growth phase.<sup>8,20</sup>

The oral melanotic macule is a small, well-circumscribed, brown-to-black that occurs commonly on the lips and gingiva, followed by the palate and buccal mucosa. Patients age ranges from 4 to 98 years (mean 43.7) with predilection for females (1.9:1).<sup>8</sup>

Hyperpigmentation of the palate by antimalarial drugs has been mainly reported in hard palate, rarely involving other sites of the mouth such as gingiva, lips and buccal mucosa. Some adverse cutaneous reactions have also been reported with the use of antimalarial medications, such as psoriasis, pruritus, rashes, alopecia, hair bleaching, dry skin, allergic contact dermatitis, Stevens-Johnson like syndrome and photosensitivity.<sup>21</sup>

Microscopically, chloroquine-induced hyperpigmentation shows subepithelial deposition of melanin and/or hemosiderin which are characterized as Fontana-Masson and Perls' reactions. Melanocytes stimulation during use of antimalarial drugs occurs by elevating levels of androgens, which in turn stimulate melanocytes. Hemosiderin deposition occurs by iron chelation by the drug or its metabolite.<sup>17,22</sup> Notably, in the present cases the medical history revealed no use of any medication, and the hypothesis of drug-associated hyperpigmentation was excluded.

Table 1 summarizes the most common findings reported about oral Blue Nevus, describing 36 cases. Most of the cases reported were on males. We reported 1 case in a male and 1 in a female. The population described was from all ages, showing that Blue Nevus can occur at any moment in life. In both cases reported in the present study the patients had 32 and 36 years old. Some authors also reported the race of the patients, which showed a high incidence in white population. Buchner, 1987<sup>18</sup> reported 4 cases of Blue Nevus in Hispanic descent patients. The patients of the cases presented in this study are Hispanic. As for the most common locations of the lesion it is noted a higher prevalence in hard palate and a few reports on oral mucosa<sup>3,23</sup>, upper labial and vermilion border of the lip.<sup>18</sup> Both cases present here occurred in hard palate. One study<sup>24</sup> reported 1 case of Blue Nevus on floor of the mouth. The different clinical aspects of the lesions described were flat and raised. One author described the lesion as slightly elevated<sup>25</sup>, one described as just swelling<sup>24</sup> and other described as dark blue, firm, sessile mass.<sup>3</sup> As for the sizes of the Blue Nevus lesions described, it was observed that the smallest ones measured 1 mm and the biggest one, reported by Buchner<sup>18</sup>, measured 20 mm. Blue Nevus usually measures between 2 and 10 mm in diameter.<sup>2,3</sup> Both cases reported in the present study were flat macules, one measuring 13 x 6 mm and the other 5 x 3 mm, being coincident with the average sizes reported so far.

Blue Nevus is typically identified during the fifth decade of life<sup>2,11</sup> but it's also common during the third decade, which coincides with both the cases described in this report. Buchner<sup>11</sup>, also described Blue Nevus as being more common in men, while all other types of nevi were more common in women. Here we described one case for each gender.

Pennacchiotti<sup>26</sup> carried out a study in 2018, with the aim of investigating pigmented lesions in the oral mucosa of 10 children and adolescents. The authors found that the lesions affected boys and girls equally and the most affected area was the gingiva, followed by the palate.

The most extensive lesion measured 0.8 cm and had diffuse borders corresponding to a blue nevus. There are few reports of solitary pigmented lesions of the oral mucosa of children and adolescents, so it is difficult to determine their frequency and there is no guidance on when biopsy is indicated.<sup>26</sup> Junctional nevus and blue nevus have been reported more frequently in young people.<sup>11</sup> In the work by Kaugars<sup>27</sup> it was observed that pigmented lesions located in the lower lip and gingiva had a lower mean age than those present in other places in the oral cavity.

Histologically, Blue Nevus is characterized by presence of melanocytes, singly or in small aggregations, a variable degree of fibrosis and dermis deformation. Usually there is presence of melanophages as predominant cells.<sup>25</sup>

Because Blue Nevus is not recognized more frequently, the diagnosis may result in confusion with pigmented nevi or mistaken for a malignant melanoma.<sup>28</sup> Histologically, the melanocytic nevus presents increased melanin produced by basal melanocytes which are morphologically normal. Melanin pigment is also observed in melanophages in the upper portion of the lamina propria.<sup>8,29</sup> Melanocytic nevus' proliferation is characterized by proliferation of benign neoplastic melanocytes along the epithelial-mesenchymal junction, migration of these cells into the mesenchymal compartment (compound nevus) and loss of the junctional component of the nevus.<sup>29</sup> Oral melanoacanthoma on histological examination, presents a fine black granular or fibrillar material embedded in the connective tissue or in a perivascular location with little or no inflammatory response is seen.<sup>8</sup>

So, due to the rarity of the Blue Nevus, accurate diagnosis is crucial. Studies suggest that, malignant nevi are larger than 30mm, present nuclear pleomorphism, atypical mitosis, necrosis and destructive and expansive growth.<sup>13</sup>

By reporting these two cases, this study intends to support the professionals both in directing precise clinical conduct and in the quality of patient care, which might be helpful in the monitoring and management of pigmented lesions. More than a century after its initial description, in 1906, blue nevus remains a current and controversial topic, mainly due to the wide variety of pigmented lesions reported, as well as other diagnostic and therapeutic possibilities.

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## CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interests related to this study.

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