



A Patient with a Sudden Onset of Oral Pigmentation

Jack Botros¹ and Firoozeh Samim^{1*}

Affiliation: ¹Department of Dentistry, McGill University, Canada

***Corresponding author:** Firoozeh Samim, Assistant Professor, Faculty of Dentistry, McGill University, 2001 McGill College, RM 502, Montreal, Quebec H3A 1G1, Canada, E-mail: firoozeh.samim@mcgill.ca

Citation: Botros J and Samim F. A patient with a sudden onset of oral pigmentation (2020) Dental Res Manag 4: 60-65.

Received: Nov 04, 2020

Accepted: Nov 27, 2020

Published: Dec 08, 2020

Copyright: © 2020 Botros J, et al., This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Addison's disease or primary adrenal insufficiency (hypoadrenocorticism) is an endocrine disease characterized by a deficiency in the production of the adrenal cortex hormones, particularly cortisol and aldosterone. Patients affected by Addison's disease develop anorexia, weight loss, hypoglycemia, fatigue, nausea, vomiting, skin, and mucosal pigmentation. Skin pigmentation is considered a commonly encountered manifestation of the disease; however, oral mucous membrane pigmentation is rarely noticed early enough for diagnosis. This case report demonstrates a case where oral pigmentation was an early diagnostic sign of Addison's disease.

Keywords: Oral medicine, Diagnosis, Oral, Pigmentation, Addison disease

Clinical Presentation

A previously healthy 58-year-old female patient was presented for a routine dental examination. On clinical examination asymptomatic multifocal brownish macules ranging from 3 to 6 mm were found on the right and left buccal mucosae and the upper labial mucosa (Figure 1). Extra-oral examination revealed non-palpable sub-mandibular, sub-mental and cervical lymph nodes as well as a normal peri-oral skin and light brown complexion. The comprehensive medical history revealed a recent history of nausea, fatigue, and decreased appetite during the preceding month. The patient was unaware of the onset of the discovered pigmentations. The vital signs were measured revealing normal temperature, blood pressure, respiratory rate, and pulse. The patient was a non-smoker and a non-alcoholic.

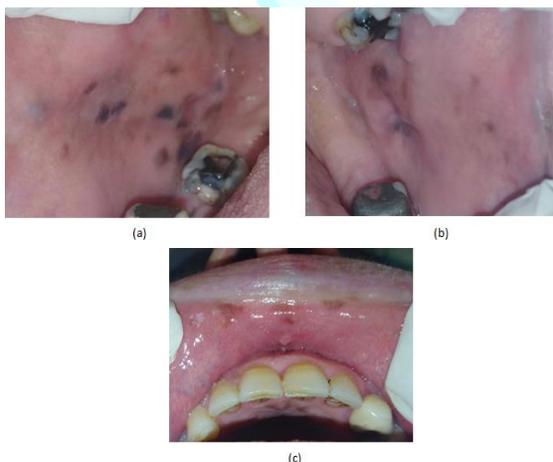


Figure 1: 58-year-old female with multifocal pigmentation attributed to Addison's disease on: (a) the left buccal mucosa, (b) the right buccal mucosae (c) the upper labial mucosa.

Differential Diagnosis of Oral Pigmented Lesions

The differential diagnosis of oral pigmentation includes a wide range of both focal and multifocal or diffuse pigmentation. Most of the oral pigmented lesions are benign and require simple assurance. However, malignant pigmented lesions such as malignant melanoma and Kaposi's sarcoma could be encountered. In addition, oral pigmentation could be a sign of an underlying systemic disease [1-3].

In order to evaluate a particular oral pigmented lesion a comprehensive dental and medical history should be taken from the patient as well as extraoral and intraoral examinations. In some cases, laboratory investigations could be useful to confirm the diagnosis. The medical history should include the onset, and Location of the lesion, any associated constitutional symptoms such as fatigue, malaise, anorexia, weight loss), drug intake, and habits such as smoking and alcohol consumption. The patient should be asked for any extra oral skin or mucosal pigmentations, particularly, in the peri-oral region and the genitalia. The intraoral examination includes an assessment of the distribution (i.e. unilateral or bilateral), pattern (i.e. focal, multifocal or diffuse), size, and color of the lesion. If the lesion was blood-filled, diascopy test is used to determine whether it was intravascular or extravascular. In this paper we propose an algorithm (Figure 2) to be followed for the assessment of most oral pigmented lesions based on the history and the clinical presentation.

Focal Pigmented Lesions

Oral/ labial melanotic macule is the most common oral melanotic lesions. It usually develops on the lower lip (labial melanotic macule) and the gingiva. It can also occur elsewhere in the oral mucosa. In most cases, melanotic macules are small (<1 cm) and well defined which does not enlarge, once reached a specific size. Microscopically, melanotic macules show an abundance of melanin pigment in the basal cell layer, which is often, accentuated at the tips of the rete pegs. It is not associated with melanocyte proliferation. Thus, it is totally benign and is not known to transform into malignant melanoma (Figure 3) [4-7].

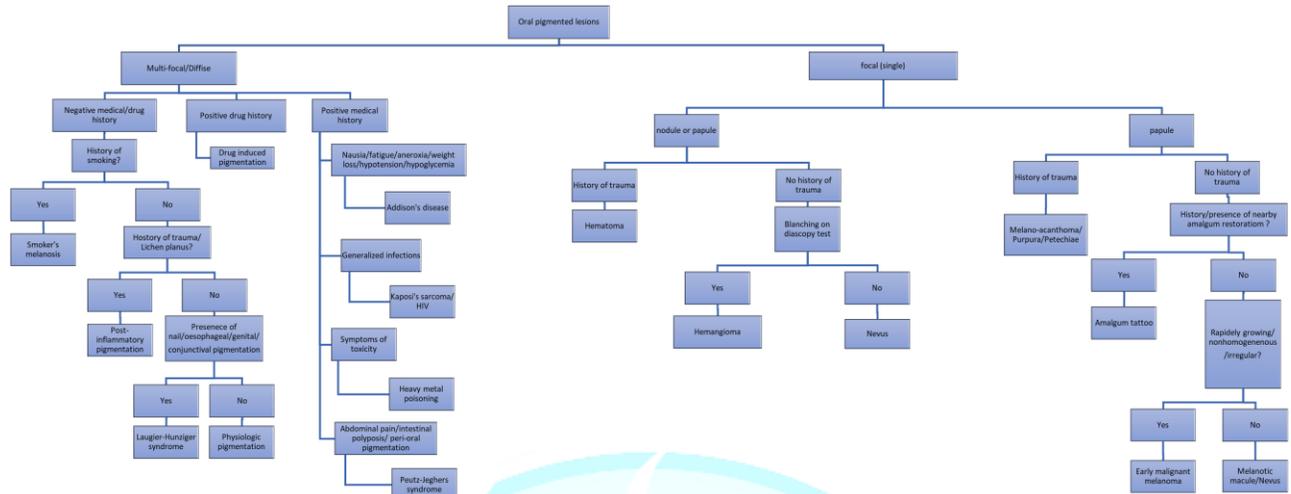


Figure 2: An algorithm for the evaluation of pigmented lesions of the oral cavity.

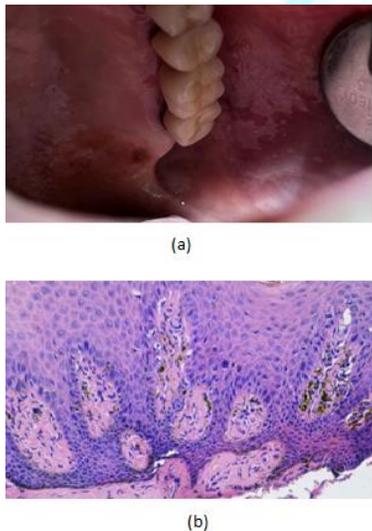


Figure 3: (a) 78 year old female with oral melanotic macule on the left hard palate, palatal to tooth 2.6 (b) Histopathological examination showed melanin pigmentation and melanin incontinent in the connective tissue.

Melanocytic nevus is a rare cause of focal oral pigmentation. It can be classified into junctional, compound, intramucosal, and blue nevi. Junctional nevi presents mostly as a brown to black macule while compound and intramucosal nevi might be lighter in color, dome-shaped, and most commonly seen in the buccal mucosa. Blue nevi develop deep in the connective tissue which may account for its color and develop most commonly in the palate. Histologically melanocytic nevi develop from the benign proliferation of melanocytes. They are believed to have precursor cells that may transform into malignant melanoma. For this reason, nevi, particularly, in the palate should be biopsied (Figure 4) [4,8-10].

Amalgam tattoo is the most common pigmented lesion in the oral cavity. It appears as a grey-blue macule most commonly on the gingiva, alveolar mucosa, and buccal mucosa. Amalgam tattoo may be introduced through a variety of dental procedures by which amalgam particles can be carried into a laceration or an extraction socket or even intact mucosa. Diagnosis could be made on the basis of radiographic examination when the amalgam particles are large

enough. In this case, fine radio-opacities could be observed. If not possible and it is in a suspicious location such as the hard palate, taking a biopsy is advised to rule out malignant neoplasm. Under the microscope, fine black granules or fibrils are seen embedded in the connective tissue with little or no inflammatory reaction (Figure 5) [2,4,5,11,12].

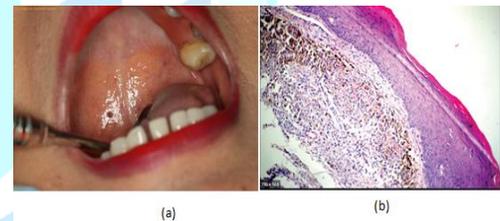


Figure 4: (a) 49 year old female with brown-black papule on the hard palate (intramucosal nevus) (b) Histopathologic examination shows Nevus cells with pigmentation under the epithelium and nests of epithelioid melanocytic nevus cells.

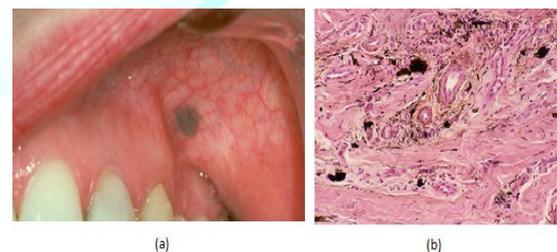


Figure 5: (a) 37 year old female with a blue macule on the left buccal mucosa (b) the histopathological examination shows pigmented particles in the connective tissue staining the connective tissue fibers.

Oral melanoacanthoma is a reactive benign pigmented lesion that usually has an acute onset in response to trauma or local irritation, frequently in dark skin population. Clinically, it is brownish in color, has ill-defined margins, and enlarges rapidly. Thus, a biopsy is mandatory to exclude malignancy. The most common site of oral melanoacanthoma is the buccal mucosa. On microscopic examination, it shows the proliferation of the benign dendritic melanocytes in the acanthotic and the spongiotic layers of the epithelium (Figure 6) [4,8,13,14].

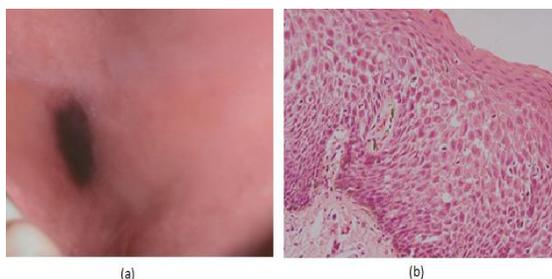


Figure 6: (a) 36 year old male with brown-black macule on the left buccal mucosa. (b) The histopathological examination shows acanthosis and spongiosis with dendritic melanocytes throughout the epithelium.

Hemangioma is the proliferation of vascular endothelial cells. Hemangiomas occur to 4-5% of infants aging 1 year, making it the most common tumor of infancy. It is an elevated lesion whose color ranges from red to blue or purple. Diagnosis is often based on blanching with a diascopy test. This test is performed by applying gentle pressure on the lesion by using a glass slide. Blanching indicates an intra-vascular lesion (**Figure 7**) [2,15,16].

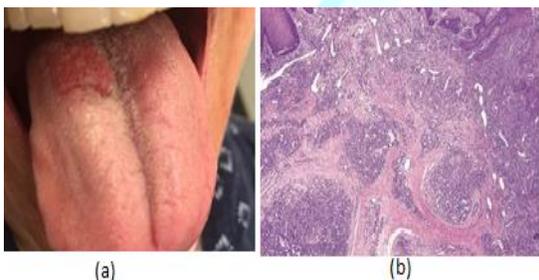


Figure 7: (a) 29 year old female with a red papule on the tongue. (b) The histopathological examination shows lobular architecture of vessels with many dilated capillaries.

Varix is defined as abnormally dilated veins observed in old individuals. This most common site of varix is the ventral surface of the tongue where they appear as small soft purplish granules that blanch on diascopy test (**Figure 8**) [2].



Figure 8: Sublingual varix in 75-year old male.

Hematoma, petechiae, purpurae, and ecchymoses are extravascular lesions caused by the extrusion of blood into the connective tissue following a traumatic event. The color of these lesions will appear red initially and turns into brown gradually as a result of the degradation of hemoglobin in the extravasated red blood cells into hemosiderin and usually disappears within 2 weeks. The differentiation between these lesions is upon clinical examination. Hematoma is an elevated lesion, while petechiae, purpurae, and ecchymoses are flat and differ only in their sizes. Petechiae are characterized by being pinpoint. The diameter of purpura ranges from 2 mm to 2 cm, while ecchymosis is larger than 2 cm in diameter (**Figure 9**) [2,4,16,17].



Figure 9: Hematoma and petechias in a 26 year old patients with leukemia.

Malignant melanoma is a rare oral cancer representing less than 1% of oral malignant tumors. It is a malignant proliferation of melanocytes in the junction between the epithelium and the connective tissue as well as in the connective tissue. The most common site of oral melanoma is the hard palate followed by the maxillary gingivae which together represent two thirds of the cases. Oral melanomas are usually encountered between the fifth and the seventh decades of life and in black-skinned individuals, who have 3 to 4 times more risk than whites. It presents as a black or brown slowly-growing patch with a non-homogeneous color and ill-defined borders or a rapidly-enlarging mass associated with bleeding ulceration and pain. However, up to one third of the cases exhibit no pigmentation (amelanotic) (**Figure 10**) [2,4,8,10, 17-19].

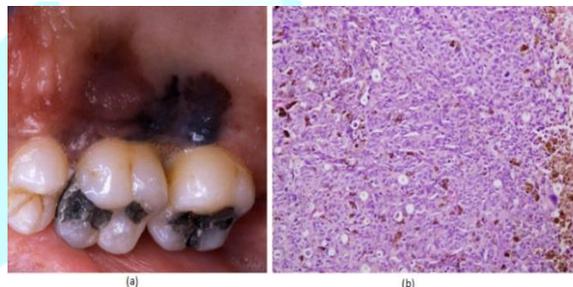


Figure 10: (a) Oral melanoma on a posterior hard palate. (b) Histopathological exam shows nest of malignant melanocytic cells with the pigmentations.

Multi-Focal/Diffuse Pigmentation

Physiologic (racial) pigmentation is the most common multi-focal or diffuse oral pigmentation. It is more common in dark-skinned individuals such as Africans, Asians, and South-Americans. Physiologic pigmentation usually appears during the first two decades of life, but may not be noticed by the patient until adulthood. The attached gingiva is the most commonly affected site, although pigmentation of the labial and buccal mucosae is not uncommon where it appears usually as ill-defined patches. On the microscopic level, increased melanin pigment within the basal cell layer can be observed. Physiologic pigmentation could be considered as a differential diagnosis for the presented case, provided that the patient had a brown complexion (**Figure 11**) [2,4,8,20].



Figure 11: Physiological pigmentation involving the gingiva.

Drug-induced melanosis is a common cause of multi-focal or diffuse oral pigmentation. A number of drugs may cause this type of pigmentation including antimalarials such as chloroquine, hydroxychloroquine, and quinacrine. These drugs are also used for autoimmune diseases. Other examples of drugs related to oral melanosis are minocycline, tetracycline, oral contraceptives, and cytotoxic medications such as cyclophosphamide and busulfan. There are multiple mechanisms for drug-induced oral pigmentation. According to the type of the drug used, it may include the accumulation of melanin, the deposition of the drug itself or one of its metabolites, a drug-induced synthesis of pigments such as lipofuscin, or the deposition of iron due to vessels damage and red blood cells lysis. In our presented case, the patient did not give a history of any drug intake; thus, drug-induced melanosis was excluded from the differential diagnosis (**Figure 12**) [4,17,20-23].



Figure 12: Hydroxychloroquine induced pigmentation on palate of a 37-year old female with systemic lupus erythematosus.

Smoker's melanosis occurs most commonly in the labial gingiva followed by the buccal mucosae and the palate of smokers. Up to 21.5% of smokers demonstrate this type of pigmentation with females being more affected than males. Smoker's melanosis appears as flat brown map-like or geographic areas. In dark-skinned individuals showing physiologic pigmentation, smoking may accentuate the oral pigmentation. Despite caused by smoking, smoker's melanosis is not potentially malignant and returns to normal after cessation of smoking. Since our case was a non-smoker, this was not considered as a differential diagnosis as well (**Figure 13**) [4,8,24-27].

Post-inflammatory (inflammatory) pigmentation appears simultaneously or following injuries or long-standing inflammatory diseases, particularly, lichen planus. Clinically, diffuse brown pigmented areas are seen in proximity to reticular, erosive, or vesicular lesions. This is more common in individuals with a dark complexion. Histologically, there is increased basilar melanin and melanin laden macrophages in the connective tissue. The clinical examination of the reported case did not reveal any inflammatory disease underlying the pigmentation. Also there was no history of injury or trauma (**Figure 14**) [2,8, 28].



Figure 13: (a) Brown pigmentation on the lip same area of holding the smoking. (b) Histopathological examination shows melanocytic hyperplasia, vascular ectasia, and mild chronic inflammation and melanin pigmentations.



Figure 14: Post inflammatory pigmentations in a patient with oral lichen planus.

Kaposi's sarcoma (could be solitary in the oral cavity) is a multifocal vascular malignancy that develops at the late stages of Human Immunodeficiency Virus (HIV) disease and is considered the most common neoplasm in AIDS patients. In one study 45% of AIDS patients had oral Kaposi's sarcoma. Another study reported that 27 out of 53 AIDS-related Kaposi's sarcoma occurred in the oral cavity. Early Kaposi's sarcoma appears as red to brown macules or patches which are often bilateral. In the late stages it becomes nodular, bleeding, and ulcerating. It usually occurs in the palate, gingiva, or the tongue. Our patient did not have any sign of AIDS, therefore, Kaposi's sarcoma was excluded (**Figure 15**) [2,17,18,29,30].

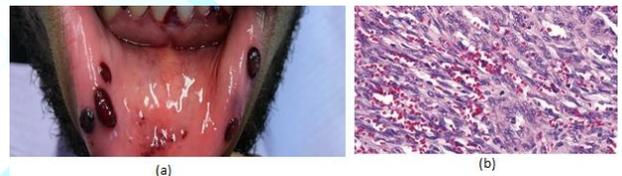


Figure 15: (a) Multiple Kaposi sarcomas of the oral cavity.

(b) Histopathological examinations shows cellular proliferation of spindle cells surround slit-like spaces with polymorphism, atypia and mitotic activity.

Peutz-Jeghers Syndrome is a rare autosomal dominant disease associated with mutations in the LKB1/STK11 gene located on the short arm of chromosome. It is characterized by generalized or multiple small brownish macules on the lower lip and in the perioral region. Intranasal, conjunctival, and intraoral pigmentation can also be seen. Clinical manifestations include intestinal polyposis and increased risk of gastrointestinal cancer. This was not considered in our top-suspected diagnoses due to the absence of any abdominal symptoms or perioral pigmentation and late acute onset [8,19,31-33].

Laugier-Hunziker pigmentation is an idiopathic pigmentation described as macular hyperpigmentation of the oral mucosa, particularly, the labial and buccal mucosae. Other mucosal surfaces can also be affected such as the esophageal, genital, conjunctival mucosae. In addition, 60% of patients exhibit nail pigmentation in the form of melanotic streaks. Laugier-Hunziker pigmentation is diagnosed by exclusion when all other potential causes of oral pigmentation are eliminated. For this reason, it was considered as the last differential diagnosis, in case other suspected diagnoses are excluded [4,34,35].

Addison's disease or primary hypoadrenalism is caused by the progressive destruction of the adrenal glands. Autoimmune disease is one of the most common etiologies of this destruction, together with neoplasms, trauma, medications, infection and iatrogenic causes. Although weakness, fatigue, depression are the most common early presenting signs of the disease, mucocutaneous hyperpigmentation may be one of the earliest signs or even the first sign of the disease. As the levels of the adrenal cortex hormones decrease, Adrenocorticotropic Hormone (ACTH) is secreted from the anterior pituitary gland to stimulate steroids secretion from the adrenal cortex. Concurrently, α -Melanocyte-Stimulating Hormone (α -MSH) serum levels also increase resulting in a generalized tan-like appearance as



well as bilateral multi-focal oral pigmentation. The case presented in this paper reported a history of nausea, fatigue, and reduced appetite. These signs in addition to the bilateral multi-focal pattern of pigmentation in the buccal mucosae made Addison's disease one of our suspected differential diagnoses [2,4,35-38].

Given that the presented oral pigmentation followed a bilateral multi-focal pattern, focal pigmentations were excluded from our differential diagnosis. Therefore, our top differential diagnoses were:

- 1) Physiologic pigmentation being the most common diffuse or multi-focal pigmentation,
- 2) Pigmentation associated with Addison's disease, given the systemic manifestations presented such as nausea, fatigue, and reduced appetite and the unusual pattern of the pigmentation,
- 3) Laugier-Hunziger pigmentation after excluding the two aforementioned diagnoses.

Laboratory Investigations and Diagnosis

Given that pigmentation associated with Addison's disease was one of the proposed diagnoses, laboratory investigations were requested. The requested tests were: morning serum cortisol and blood chemistry. The morning serum cortisol level was below the minimum reference range (4.1 µg/dL, reference: 5-25 µg/dl). Blood chemistry as well revealed a serum sodium level (137.2 mmol/L) at the lower border of the normal range (136-150 mmol/L) and a slight hyperchloremia (106.9 mmol/L, Reference: 95-105 mmol/L). These findings suggest early Addison's disease diagnosis. The patient was referred to the endocrinology department for further investigations and management.

Discussion

Addison described the main features of her disease as: "general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of color in the skin, occurring in connection with a diseased condition of the suprarenal capsules". Primary adrenal insufficiency is known as Addison's disease, results in the reduction or the lack of the glucocorticoids (primarily cortisol) and mineralocorticoids (primarily aldosterone). The symptoms associated with the disease are attributed to the low cortisol and aldosterone levels. Reduced serum cortisol leads to hypoglycemia, weakness, and fatigue, while low serum aldosterone causes an electrolyte imbalance: decreased sodium and chloride and increased potassium. This in turn results in hypotension, weight loss, and salt craving. Addison's disease patients also present with anorexia, skin, and mucosal hyperpigmentation. Hyperpigmentation in Addison's disease is a manifestation of increased Adrenocorticotropic Hormone (ACTH) and α -Melanocyte Stimulating Hormone (α -MSH) from the pituitary gland as a feedback mechanism of adrenal failure [4,39-42].

Hyperpigmentation has been perceived as a hallmark sign of Addison's disease. Skin pigmentation can be generalized presenting as a bronze or a tan-like appearance that is difficult to detect in dark-skinned individuals. Besides, pigmentation can be more prominent in the sun-exposed areas of the skin such as the face, the neck, and the hands, also at the sites of friction, palmer creases, and recent scars. The buccal mucosa, vermilion border of the lips, gingiva, and vaginal mucosa may also exhibit areas of hyperpigmentation [37,39,40,43,44].

Evidence considered mucocutaneous pigmentation as a useful diagnostic aid for Addison's disease. This is confirmed by multiple case reports which reported mucocutaneous pigmentation as an early or the only sign of Addison's disease. Hydar et al. [45] demonstrated that in six out of seven patients with adrenal insufficiency presented with hyperpigmentation as the first symptom of the disease. Najjar and Jarrah reported a case in which tan-like skin pigmentation was the only sign of Addison's disease. Smith as well published a case report

demonstrating skin pigmentation as a diagnostic sign of the disease [4,35,43,45-47].

Although oral pigmentation is not uncommon in Addison's disease, it can be misdiagnosed as drug-induced melanosis, physiologic pigmentation, or other more common diffuse or multi-focal intra-oral pigmentation. It has been reported as well that oral pigmentation can be the sole manifestation of the disease and if diagnosed at this early stage, this can prevent its progression and the associated complications. Burk et al. [42] reported two cases of pigmentation in the labial mucosa, tongue, and gingiva. After a thorough medical history, the two cases were found to have systemic manifestations such as nausea, vomiting, and fatigue. Laboratory tests confirmed their diagnosis as adrenal insufficiency. Similarly, Lanza et al. [38] diagnosed a case with Addison's disease depending, primarily, on oral pigmentation as a diagnostic sign. Moreover, tongue and lip pigmentation were the only clinical signs for Addison's disease in a case reported by Strakosch and Gordon [48].

Conclusion

Although the diagnosis of Addison's disease before the development of systemic symptoms is rare, it should be aimed for. Addison's disease should be considered as a differential diagnosis for multi-focal and diffuse intra-oral pigmentation, particularly when associated with constitutional and systemic symptoms such as nausea, vomiting, and fatigue.

References

1. Lenane P and Powell F. Oral pigmentation (2002) J EADV 14: 448-465. <https://doi.org/10.1046/j.1468-3083.2000.00143.x>
2. Adel Kautzman B, Pavone M, Blanas N and Bradley G. Pigmented lesions of the oral cavity: review, differential diagnosis, and case presentations (2004) J Can Dent Assoc 70: 682-683.
3. Cicek Y and Ertas U. The normal and pathological pigmentation of oral mucous membrane: a review (2003) J Contemp Dent Pract 4: 76-86. <https://doi.org/10.5005/jcdp-4-3-76>
4. Burket LW, Greenberg MS, Glick M and Ship JA. Burket's oral medicine (2008) BC Decker, Canada
5. Weathers D, Corio RL, Crawford B, Giansanti J and Page L. The labial melanotic macule (1976) Oral Surg Oral Med Oral Pathol 42: 196-205. [https://doi.org/10.1016/0030-4220\(76\)90124-9](https://doi.org/10.1016/0030-4220(76)90124-9)
6. Page L, Corio R, Crawford B, Giansanti J and Weathers D. The oral melanotic macule (1977) Oral Surg Oral Med Oral Pathol 44: 219-226. [https://doi.org/10.1016/0030-4220\(77\)90272-9](https://doi.org/10.1016/0030-4220(77)90272-9)
7. Gupta G, Williams R and Mackie R. The labial melanotic macule: a review of 79 cases (1997) Brit J Dermatol 136: 772-775. <https://doi.org/10.1046/j.1365-2133.1997.6731621.x>
8. Gondak RO, da Silva-Jorge R, Jorge J, Lopes MA and Vargas PA. Oral pigmented lesions: Clinicopathologic features and review of the literature (2012) Med Oral Patol Oral Cir Bucal 17: e919. <https://doi.org/10.4317/medoral.17679>
9. Buchner A and Hansen LS. Pigmented nevi of the oral mucosa: A clinicopathologic study of 36 new cases and review of 155 cases from the literature: Part II: Analysis of 191 cases (1987) Oral Surg Oral Med Oral Pathol 63: 676-682. [https://doi.org/10.1016/0030-4220\(87\)90370-7](https://doi.org/10.1016/0030-4220(87)90370-7)
10. Hicks M and Flaitz C. Oral mucosal melanoma: epidemiology and pathobiology (2000) Oral Oncol 36: 152-169. [https://doi.org/10.1016/s1368-8375\(99\)00085-8](https://doi.org/10.1016/s1368-8375(99)00085-8)
11. Weathers DR and Fine RM. Amalgam tattoo of oral mucosa (1974) Arch Dermatol 110: 727-728. <https://doi.org/10.1001/archderm.110.5.727>
12. Müller S. Melanin-associated pigmented lesions of the oral mucosa: presentation, differential diagnosis, and treatment (2010) Dermatol Therap 23: 220-229. <https://doi.org/10.1111/j.1529-8019.2010.01319.x>



13. Goode RK, Crawford BE, Callihan MD and Neville BW. Oral melanoacanthoma: review of the literature and report of ten cases (1983) *Oral Surg Oral Med Oral Pathol* 56: 622-628. [https://doi.org/10.1016/0030-4220\(83\)90080-4](https://doi.org/10.1016/0030-4220(83)90080-4)
14. Fornatora ML, Reich RF, Haber S, Solomon F and Freedman PD. Oral melanoacanthoma: a report of 10 cases, review of the literature, and immunohistochemical analysis for HMB-45 reactivity (2003) *Ameri J Dermatopathol* 25: 12-15. <https://doi.org/10.1097/0000372-200302000-00003>
15. Neville BW, Damm DD, Allen CM and Chi AC. *Oral and maxillofacial pathol* (2016) Elsevier, United States 604-605.
16. Carpenter W and Rudd M. Focal, flat pigmentations of the oral mucosa: a clinical approach to the differential diagnosis (2000) *J Calif Dent Asso* 28: 949-954.
17. Hatch CL. Pigmented lesions of the oral cavity (2005) *Dent Clini* 49: 185-201. <https://doi.org/10.1016/j.cden.2004.07.013>
18. Eisen D and Voorhees JJ. Oral melanoma and other pigmented lesions of the oral cavity (1991) *J Ameri Acad Dermatol* 24: 527-537. [https://doi.org/10.1016/0190-9622\(91\)70077-f](https://doi.org/10.1016/0190-9622(91)70077-f)
19. Rapidis AD, Apostolidis C, Vilos G and Valsamis S. Primary malignant melanoma of the oral mucosa (2003) *J Oral Maxillofa Surg* 61: 1132-1139. [https://doi.org/10.1016/s0278-2391\(03\)00670-0](https://doi.org/10.1016/s0278-2391(03)00670-0)
20. Eisen D. Disorders of pigmentation in the oral cavity (2000) *Clini Dermatol* 18: 579-587. [https://doi.org/10.1016/s0738-081x\(00\)00148-6](https://doi.org/10.1016/s0738-081x(00)00148-6)
21. Kleinegger CL, Hammond HL and Finkelstein MW. Oral mucosal hyperpigmentation secondary to antimalarial drug therapy (2000) *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol* 90: 189-194. <https://doi.org/10.1067/moe.2000.106340>
22. Cockings JM and Savage NW. Minocycline and oral pigmentation (1998) *Austra Dent J* 43: 14-16. <https://doi.org/10.1111/j.1834-7819.1998.tb00145.x>
23. Dereure O. Drug-induced skin pigmentation (2001) *Ameri J Clini Dermatol* 2: 253-262. <https://doi.org/10.2165/00128071-200102040-00006>
24. Hedin CA. Smokers' melanosis: occurrence and localization in the attached gingiva (1977) *Archi Dermatol* 113: 1533-1538. <https://doi.org/10.1001/archderm.113.11.1533>
25. Hedin CA and Axell T. Oral melanin pigmentation in 467 Thai and Malaysian people with special emphasis on smoker's melanosis (1991) *J Oral Pathol Med* 20: 8-12. <https://doi.org/10.1111/j.1600-0714.1991.tb00879.x>
26. Axeix T and Hedin Ca. Epidemiologic study of excessive oral melanin pigmentation with special reference to the influence of tobacco habits (1982) *Europ J Oral Sci* 90: 434-442. <https://doi.org/10.1111/j.1600-0722.1982.tb00760.x>
27. Hedin C, Pindborg JJ and Axell T. Disappearance of smoker's melanosis after reducing smoking (1993) *J Oral Pathol Med* 22: 228-230. <https://doi.org/10.1111/j.1600-0714.1993.tb01061.x>
28. Halder RM and Nootheti PK. Ethnic skin disorders overview (2003) *J Ameri Acad Dermatol* 48: S143-S148. <https://doi.org/10.1067/mjd.2003.274>
29. Silverman Jr S, Migliorati CA, Lozada-Nur F, Greenspan D and Conant MA. Oral findings in people with or at high risk for AIDS: a study of 375 homosexual males (1986) *J Ameri Dent Assoc* 112: 187-192. <https://doi.org/10.14219/jada.archive.1986.0321>
30. Lozada F, Silverman Jr S, Migliorati CA, Conant MA and Volberding PA. Oral manifestations of tumor and opportunistic infections in the Acquired Immunodeficiency Syndrome (AIDS): findings in 53 homosexual men with Kaposi's sarcoma (1983) *Oral Surg Oral Med Oral Pathol* 56: 491-494. [https://doi.org/10.1016/0030-4220\(83\)90095-6](https://doi.org/10.1016/0030-4220(83)90095-6)
31. Hemminki A, Tomlinson I, Markie D, Järvinen H, Sistonen P, et al. Localization of a susceptibility locus for Peutz-Jeghers syndrome to 19p using comparative genomic hybridization and targeted linkage analysis (1997) *Nature Genet* 15: 87-90. <https://doi.org/10.1038/ng0197-87>
32. Hemminki A, Markie D, Tomlinson I, Avizienyte E, Roth S, et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome (1998) *Nature* 391: 184-187. <https://doi.org/10.1038/34432>
33. Meleti M, Vescovi P, Mooi WJ and van der Waal I. Pigmented lesions of the oral mucosa and perioral tissues: a flow-chart for the diagnosis and some recommendations for the management (2008) *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol* 105: 606-616. <https://doi.org/10.1016/j.tripleo.2007.07.047>
34. Gaeta GM, Satriano RA and Baroni A. Oral pigmented lesions (2002) *Clinics Dermatol* 20: 286-288. [https://doi.org/10.1016/s0738-081x\(02\)00225-0](https://doi.org/10.1016/s0738-081x(02)00225-0)
35. Alawi F. Pigmented lesions of the oral cavity: an update (2013) *Dent Clini* 57: 699-710. <https://doi.org/10.1016/j.cden.2013.07.006>
36. Kim H. Generalized oral and cutaneous hyperpigmentation in Addison's disease (1988) *Trop Odonto-Stomatol=Trop Dent J* 11: 87-90.
37. Nieman LK and Chanco Turner ML. Addison's disease (2006) *Clin Dermatol* 24: 276-280.
38. Lanza A, Heulfe I, Perillo L, Dell'Ermo A and Cirillo N. Oral pigmentation as a sign of Addison's disease: a brief reappraisal (2009) *Open Dermatol J* 3: 3-6. <https://doi.org/10.2174/1874372200903010003>
39. Addison T. On the constitutional and local effects of disease of the supra-renal capsules (1855) Wellcome Collection, United Kingdom.
40. Simpson SL. Addison's disease (1950) *Brit Med J* 2: 1164.
41. Ten S, New M and Maclaren N. Addison's disease (2001) *J Clini Endocrinol Metabol* 86: 2909-2922. <https://doi.org/10.1210/jcem.86.7.7636>
42. Burk CJ, Ciocca G, Heath CR, Duarte A, Dohil M, et al. Addison's disease, diffuse skin, and mucosal hyperpigmentation with subtle "flu-like" symptoms-a report of two cases (2008) *Pediatr Dermatol* 25: 215-218. <https://doi.org/10.1111/j.1525-1470.2008.00637.x>
43. Dunlop D. Eight-six Cases of Addison's Disease (1963) *Brit Med J* 2: 887.
44. Shah SS, Oh CH, Coffin SE and Yan AC. Addisonian pigmentation of the oral mucosa (2005) *Cutis, United States* 76: 97.
45. Haydar NA, Marc JRS, Reddy WJ, Laidlaw JC and Thorn GW. Adrenocortical insufficiency with normal basal levels of urinary 17-hydroxycorticoids: diagnostic implications (1958) *J Clini Endocrinol Metabol* 18: 121-133. <https://doi.org/10.1210/jcem-18-2-121>
46. Najjar SS and Jarrah A. Pigmentation in Addison's disease; A Case in which pigmentation was the only sign (1964) *Am J Dis Child* 107: 198-201. <https://doi.org/10.1001/archpedi.1964.02080060200018>
47. Smith H. Compensated adrenocortical failure (1963) *Lancet* 281: 1077-1078. [https://doi.org/10.1016/s0140-6736\(63\)92114-7](https://doi.org/10.1016/s0140-6736(63)92114-7)
48. Strakosch C and Gordon R. Early diagnosis of Addison's disease; pigmentation as sole symptom (1978) *Austra New Zeal J Med* 8: 189-190. <https://doi.org/10.1111/j.1445-5994.1978.tb04510.x>