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CASE STUDY

Unsuspected oral pigmentation in patient with systemic disease histories

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ABSTRACT

Oral pigmentation refers to a pigmented lesion on the oral mucosa, caused by one or more pigments that accumulate, resulting in tissue color change. Pigment lesions can vary in size, color, and location, and may range from benign to malignant. The role of the dentist is crucial in recognizing and classifying these lesions to facilitate proper treatment. This case report describes oral pigmentary abnormalities suspected to be indicative of an undiagnosed systemic disease. A 52-year-old woman presented with complaints of brittle teeth. Upon examination, changes in her oral mucosa were noted, and she was found to have uncontrolled type 2 diabetes mellitus, as well as a history of hysterectomy due to a tumor. Intraoral and extraoral examination revealed macular pigmentation on the mucosa and skin, particularly on the extremities. After further investigation, we concluded that early detection of polyps is important, as these patients may be susceptible to neoplasia development in areas outside the intestines. Dentists should be vigilant in recognizing a wide range of lesions that can assist in diagnosing conditions beyond oral health, to ensure patients receive appropriate treatment.

Keywords: diabetes mellitus; oral pigmentation; underlying disease

INTRODUCTION

Pigmentation comes from the Latin word “Pigment”, meaning “color or staining”. Oral pigmentation occurs in the mouth and can generally be focal, diffuse, or multifocal. These lesions can represent normal variations or indicate life-threatening systemic diseases or malignancies.[1] Oral pigmentation can be either physiological or pathological. Physiological pigmentation often occurs in people of Asian, African, and Mediterranean descent due to the naturally uneven coloration of the oral mucosa, where discoloration is caused by the accumulation of one or more pigments in the tissue.[2]

Pathological pigmentation can be classified based on its cause into exogenous and endogenous categories. Exogenous pigmentation may result from drugs, tobacco use/smoking, amalgam tattoos, or exposure to heavy metals. In contrast, endogenous pigmentation can be linked to endocrine disorders, syndromes, infections, chronic irritation, reactivity, or malignancies.[3] Diseases associated with melanosis include Peutz-Jeghers syndrome, Addison’s disease, melanotic nevus, melanoacanthoma, and melanoma.[2] Pigmentation may present as blue or purple vascular lesions, brown melanotic lesions, brown heme-related lesions, or gray-to-black discolorations. These lesions can be flat or raised.[2,3] This case report describes the presence of pigmentary abnormalities in the mouth, which are suspected to be indicative of an underlying systemic disease.

METHODS

A 52-year-old woman presented for evaluation of brittle teeth. The patient had never previously received dental treatment and denied any history of bleeding disorders. Tooth loss had occurred since the patient was diagnosed with type 2 diabetes mellitus in 2017, with an HbA1c level of 10.2%. She had been taking 2 mg of glimepiride

daily but discontinued the medication, feeling that her diabetes was not improving. She reported conducting independent random blood sugar tests at a community health center, consistently yielding results above 300 mg/dL. She also had a history of consuming sachet drinks, seldom drinking water, urinating around 10 times per day, and sometimes experiencing bedwetting. The patient had undergone two hysterectomies: the first in 2017 due to an 8 kg tumor, and the second in 2018 for a 15 kg mass.

After the second hysterectomy, she received two weeks of chemotherapy from her oncologist. A few days prior to her dental visit, she reported fatigue, weakness, weight loss, frequent nausea, vomiting, stomach pain, occasional joint pain, and rapid mood changes. She also experienced lower back pain upon waking. During the day, she had limited sweating, along with headaches, weakness, heart palpitations, and occasional fainting and tingling in her hands and feet. Additionally, she complained of a burning sensation in her mouth that extended to her throat, especially when smoking or eating spicy food. The middle fingers of both hands often became stiff when folded, making it difficult to straighten them, with a “clicking” sound when doing so. She consumed 6 tablespoons of rice per day and felt unwell or vomited if she ate more. The patient had no history of drug or food allergies, though there was a family history of diabetes mellitus. She worked as a scavenger and lived with her husband, belonging to a lower-middle-class economic group. She had smoked since elementary school, averaging one pack per day, and consumed approximately one bottle of alcohol per day until she quit 20 years ago.

On extraoral examination, pigmented macules were noted on her extremities, palms, and other body areas, though there was no pigmentation on her nails. Intraoral examination revealed angular cheilitis on her lips, leukoedema on her buccal mucosa, pigmented macules on her labial mucosa, both buccal mucosae, upper and lower alveolar ridges, and hard palate. Other findings included traumatic keratosis on the upper and lower alveolar ridges, smoker’s melanosis on

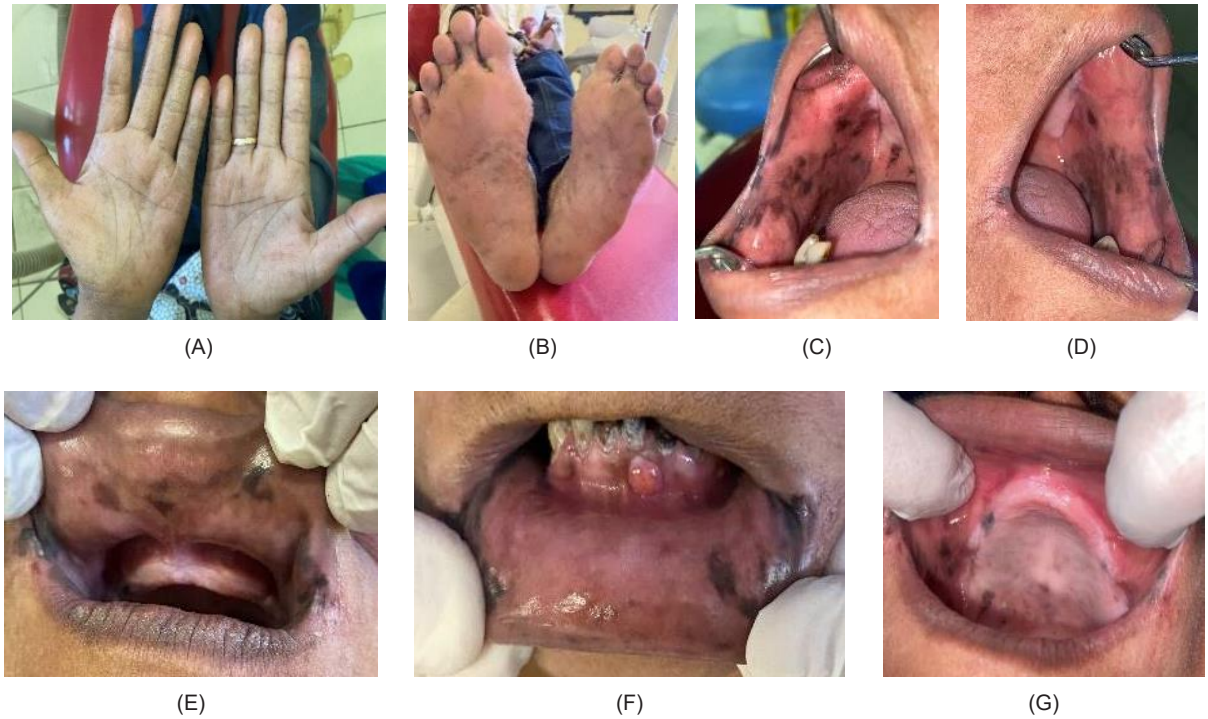

Figure 1. Mucocutaneous pigmentation on palms of the hands (A) and feet (B), left and right of buccal mucosa (C, D), upper and lower of labial mucosa (E, F), and alveolar ridge superior (G)

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the upper and lower gingivae, nicotine stomatitis on the palate, and a hairy tongue (Figure 1).

The patient was referred for routine diabetes mellitus management and advised by internal medicine to undergo regular blood tests to monitor her systemic condition. Blood test results showed hemoglobin at 21.4 g/dL (normal: 10.85-14.9 g/dL), hematocrit at 63% (normal: 34-45.1%), erythrocytes at 7.1 × 10^6/µL (normal: 4.11-5.55 × 10^6/µL), leukocytes at 3.22 × 10^3/µL (normal: 4.79-11.34 × 10^3/µL), platelets at 111 × 10^3/µL (normal: 216-451 × 10^3/µL), and cortisol at 10.5 µg/dL (normal: 3.7-19.4 µg/dL). Hemoglobin, hematocrit, and erythrocyte values were elevated, while leukocyte and platelet counts were below normal. A hematologist analyzed these findings and suspected polycythemia vera, indicated by elevated hemoglobin and hematocrit levels. However, internal medicine did not prescribe specific medication and opted for observation, recommending follow-up blood tests after two weeks. The subsequent blood test showed that the patient's hemoglobin, hematocrit, and erythrocyte levels had nearly returned to normal. The patient also underwent a JAK-2 test for polycythemia vera, which came back negative, ruling out the diagnosis of this blood disorder.

After evaluation by internal medicine, the patient returned to the oral medicine department. Intraoral examination revealed pigmentation spread throughout the mucosa, extremities, and other body areas, but none on her nails. Based on these findings, we suspected Peutz-Jeghers syndrome or Laugier-Hunziker syndrome. A definitive diagnosis could be confirmed with an STK-11 genetic test or endoscopy, but the patient lacked the financial means for these procedures. As a result, she continued with routine diabetes management in preparation for tooth extractions. Informed consent for the case report was obtained from the patient.

DISCUSSION

Pigmentation is the process of pigment deposition in tissue. Various diseases can cause mucosal discoloration, originating from intrinsic or extrinsic factors, which can be either physiological or pathological. Dentists must be aware of various lesions to help plan appropriate treatment.[3] Pigmentation may result from local accumulation of melanin, hemosiderin, or exogenous metals or indicate a systemic disorder. Diagnosing pigmented lesions can be complex, requiring differential diagnosis. A biopsy, as a supportive examination helps diagnose local lesions. An anamnesis is needed to obtain a lesion history, especially when the pigmentation lesion is likely to spread. A thorough examination of the pigmentation and a complete clinical history is necessary for early diagnosis and prompt and effective treatment. While only a few lesions have been reported to undergo malignant transformation, it is advisable to refer to a specialist if there is diagnostic uncertainty.[2] Skin and mucosal hyperpigmentation may present as amalgam tattoos, naevus, malignant melanoma, Kaposi's sarcoma, Addison's disease (AD), McCune Albright syndrome (MAS), Laugier Hunziker syndrome (LHS), or pigmentation due to drugs such as minocycline, antimalarials, and phenothiazines.[4,5]

In this case, the patient is scheduled for extraction, but is advised to undergo a laboratory examination due to related diabetic condition. During a follow-up visit, the patient presented random blood sugar levels (193 g/dL) and routine blood tests showing hemoglobin at 21.4 g/dL (normal range: 10.85-14.9 g/dL), hematocrit at 63% (normal: 34–45.1%), erythrocytes at 7.1 million/µL (normal: 4.11–5.55 million/µL), leukocytes at 3.22 million/µL (normal: 4.79–11.34 million/µL), and platelets at 111 (normal: 216–451 thousand/µL). Based on these results, the doctor suspected polycythemia vera (PV), noting elevated hemoglobin, hematocrit, and erythrocyte levels, while leukocytes and platelets were below average. JAK2 is a cytoplasmic tyrosine kinase mediating signals from cytokine receptors to the nucleus. JAK2 mutations are present in 95% of PV cases and over 50% of thrombocytopenia cases. In classic PV, the JAK2V617F mutation is typical, but its absence in some PV cases

remains unexplained. PV is a myeloproliferative disorder characterized by excessive proliferation of erythrocytic elements, granulocytic cells, and megakaryocytes. PV has diagnostic criteria such as an an RBC count of 6 to 12 million/mm³, with a hemoglobin concentration of 18 to 24 g/dL, leading to increased blood viscosity and thrombosis.[6] PV is a rare disease, with a minimum incidence of 2.6 per 100,000. In early 2005, Janus Kinase 2 (JAK 2) mutations were associated with PV, thrombocytopenia, and myelofibrosis. JAK is a cytoplasmic tyrosine kinase mediating signals from cytokine receptors to the cell nucleus.

The mutation frequency using sensitive detection techniques in peripheral blood or bone marrow is estimated to be 95% for PV and greater than 50% for thrombocytopenia. In classic PV, a JAK2V617F mutation is present, and several patients with other MPDs, such as Idiopathic Myelofibrosis (IMF) and thrombocythemia, also express the JAK2V617F mutation. The molecular basis of JAK2V617F negativity in PV remains unknown. Jalowiec concluded that searching for causes of unmutated JAK2 polycythaemia is complex and, in one third of the patients, a cause may not be found.[7] Oral manifestations in PV patients include pale mucosal or purplish red discoloration of the tongue and oral mucosa, keratosis, other forms of candidosis, mucosal ulcers, gingival bleeding, and varying degrees of gingival enlargement.[8] In this case, the patient underwent a JAK2V61F examination to prove the presence of a PV blood disorder; however, the results of the specific examination for polycythemia vera were negative, ruling out a diagnosisof polycythemia vera.

During intra- and extraoral examination, the patient showed oral pigmentation suggestive of Peutz-Jeghers syndrome (PJS), a rare autosomal dominant disorder related to mutations in the serine/threonine kinase 11 (STK11)/liver kinase B1 (LKB1) gene-related genodermatosis with a reported incidence of 1/25,000 - 1/280,000 people/year.[5] Mucocutaneous pigmentation in PJS rarely appears at birth but typically manifests in infancy or early childhood, persisting into puberty. Oral lesions usually persist, while skin and lip pigmentation tends to fade from the third decade onwards.[9] In this case, the patient, however, could not recall when the pigmentation first appeared.

PJS is characterized by hamartomatous polyps in the intestine, associated with a pattern of macular melanin deposition in the skin and mucocutaneous cavity in the oral cavity, nose, buccal cavity, and hands at 95%.[10] Brownish macules (1–5 mm in diameter) often appear on the lips and oral mucosa, especially the buccal mucosa, gums, and hard palate. Slightly more prominent pigmented macules may occur on the palms, soles, fingers and toes, and sometimes in the external genitalia.[9] Smaller and darker macules can also be found around the mouth, nose, and eyes.[9]The color change in the mucocutaneous area corresponds to those observed in the patients in this case. Clinically, PJS is characterized by oral hyperpigmentation, especially on the mouth and lips, as well as on the skin and mucosa. Additionally, benign hamartomatous polyps in the gastrointestinal mucosa can cause local bleeding, occlusion, intussusception, and post-resection small bowel syndrome. PJS is also associated with an increased risk of small bowel cancer, typically appearing in the third decade of life, and a 76% higher cumulative risk of non-gastrointestinal tumors compared to the global population in developing countries, with a higher prevalence among women. These tumors may include ovarian/testicular neoplasia, as well as pancreatic and gynecological cancers (breast, uterus, ovary) A skin biopsy of the pigmented areas usually shows increased pigmentation of basal layer keratinocytes without an increase in melanocytes. The patient's condition is similar, as they had a uterine tumor accompanied by pigmentation in the oral mucosa and extremities.[5] PJS usually begins in early adolescence and is often accompanied by intermittent abdominal pain, indicating the presence of gastrointestinal polyps.[10]

Suggestive PJS-related pigmentation requires STK11 for genetic testing. A cellular biopsy of pigmented skin shows increased pigmentation of basal layer keratinocytes without an increase

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in melanocyte increase. [9] WHO clinical pathology criteria for diagnosing PJS include: (1) three or more polyps with a histopathological picture of PJS; (2) family history of PJS with polyps; (3) family history of characteristic mucocutaneous pigmentation; and (4) characteristic mucocutaneous pigmentation with multiple polyps.[11]

Hamartomatous polyps primarily affect the small intestine (78%), but they may also develop in the large intestine (42%), stomach (38%), and rectum (28%). It may also occur in several parts of the gastrointestinal tract outside digestion, such as the renal pelvis, bladder, ureters, lungs, nose, or gallbladder. Malignancies can also occur extraintestinally, affecting organs such as breast, ovaries, cervix, fallopian tubes, thyroid, lungs, gallbladder, bile ducts, pancreas, and testicles.[10] Studies suggest that PJS patients have an increased risk of gastrointestinal (GI) and non-GI malignancies. A meta-analysis of six studies involving 210 patients revealed a cumulative 93% lifetime risk of malignancy between the ages of 15 and 64, with a 15-fold increased risk of neoplasia compared to the general population. Female PJS patients are at particularly high risk for gastrointestinal, gynecological, ovarian, cervical, uterine, and breast cancers.[9]

In this case, the patient's oral pigmentation may have been related to diabetes mellitus, which had been diagnosed five years earlier. Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. [12] Studies have shown a higher prevalence of oral pigmentation in patients with type 2 diabetes (15.2%) than in non-diabetic patients (11.1%).[13] The results are conflicting because some literature showed an increased prevalence of pigmentation in type 1 diabetes patients compared to type 2, while other studies do not. Several studies indicate oral mucosal conditions associated with diabetes mellitus include traumatic ulcers, actinic cheilitis, melanin pigmentation, fissured tongue, geographic tongue (benign migratory glossitis), leukoplakia, lichen planus, and other lichenoid lesions.[12]

The literature suggests that immune dysfunction, a cause of diabetes mellitus, can manifest as a chronic pro-inflammatory state that responds to metabolic and hemodynamic disorders. Some cases can develop into autoimmune diseases such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anemia.[12] One such condition that can lead to pigmented lesions in the oral cavity is Addison's disease, which is a rare form of primary adrenal insufficiency caused by damage to the adrenal cortex, usually from an autoimmune process.

Common clinical manifestations of Addison's disease include fatigue, weight loss, orthostatic hypotension, skin and mucosal hyperpigmentation, nausea, vomiting, abdominal pain, decreased libido, depression, and salt craving, depending on the deficiency of glucocorticoids, mineralocorticoids, or androgens. In Addison's disease, hyperpigmentation spreads to the buccal area, conjunctiva, and genital mucosa and the nail beds, palmar creases, and nipples. Most of the manifestations are nonspecific and slowly progressive, making the diagnosis of Addison's disease often difficult or delayed. However, hyperpigmentation, caused by excess binding of ACTH and alpha-melanocyte-stimulating hormone to the melanocortin 1 receptor, is a characteristic feature and diagnostic clue for Addison's disease.

Diffuse hyperpigmentation may also be caused by drugs (e.g., chemotherapy agents, antimalarial drugs, oral contraceptives, prostaglandin agonists, amiodarone, minocycline) as well as endocrine and metabolic diseases (hyperthyroidism, diabetes mellitus, hemochromatosis). In this case, there is no connection between the patient's condition and Addison's disease.[14] Her cortisol laboratory test was normal 10.5 µg/dL (3.7 – 19.4 µg/dL), ruling out the Addison's disease. Similarly, the patient denies using drugs that can cause hyperpigmentation, such as aminoquinoline, which induces blue-gray pigmentation on the pretibial surface, oral mucosa, sclera, and subungual area, or minocycline, which causes three patterns

of discoloration: general brown discoloration, dark blue discoloration limited to acne scars or areas of inflammation, and blue-gray pigmentation on the front of the lower extremities. However, the use of chemotherapy agents within two weeks after hysterectomy should be considered in the differential diagnosis of the pigmentation observed.

McCune-Albright syndrome (MAS) is an endocrine disorder accompanied by hyperfunction and focal appearance of hyperpigmentation, including café au lait macules (CALM). Abnormally pigmented macules on the face and hands are common findings during a skin examination.[14] A clinical diagnosis of MAS can be made if the following three criteria are met: (1) fibrous dysplasia, affecting 75% of the skeleton, causing slow and progressive bone growth and leading to fractures and pathological abnormalities in several bones, (2) large, irregular café-au-lait spots with serpiginous borders on the buttocks, chest, back, shoulders, neck, and other areas, typically occurring unilaterally; and (3) endocrinopathies such as precocious puberty, hyperthyroidism, acromegaly, Cushing's syndrome, or phosphate-secreting kidney disease.[15] No polyostotic fibrous dysplasia was found in this case, thus ruling out MAS.

Laugier-Hunziker syndrome (LHS) is a sporadic condition characterized by asymptomatic diffuse macular hyperpigmentation of the oral cavity and lips, accompanied by longitudinal melanonychia of the nails. It predominately affects women with a ratio of 2 : 1, although current data suggests an equal incidence in men and women, with no known familial factors.[4] In LHS, irregular lenticular hyperpigmented macules of 2-5 mm in diameter, can appear dark brown, with clear or unclear borders, occurring singly or in groups and sometimes merging. These lesions are found intraorally on the lower lip, hard and soft palate, and buccal mucosa, as well as extraorally on the palms, fingertips, andgenital area. Some lesions may progress overtime.[4]

A key feature of LHS is longitudinal melanonychia, which presents as benign longitudinal pigment bands on the nails, varying in intensity without associated nail dystrophy.[4] Baran identified three patterns of nail pigmentation in LHS: longitudinal lines 1–2 mm wide, lines 2–3 mm wide along the lateral part of the nail plate, and homogeneous pigmentation on the radial or ulnar half of the nail. Veraldi added a fourth possibility: complete nail pigmentation. Any of these patterns may affect one or more fingernails and toenails, with fingernails being more commonly affected. Not all patients with LHS exhibit both oral and nail involvement; the latter occurs in approximately 60% of cases.[4] Skin disorders in LHS are not associated with an increased risk of endocrine or non-endocrine tumors.[4] Histological examination of LHS lesions shows increased melanin deposition in basal layer keratinocytes, dermal pigment incontinence, and an increased number of melanophages in the papillary dermis, without an increase in melanocytes.[4] In this case, the patient did not exhibit nail pigmentation. Given her history of diabetes mellitus and uterine tumors, the pigmentation is unlikely to be related to LHS.

CONCLUSION

Oral Pigmentation is defined as discoloration of the mucosa, which can arise from intrinsic and extrinsic factors and may be either physiological or pathological. The presence of pigmentation on the lips, buccal and perioral mucosa may be associated with several syndromes, such as Peutz-Jegher Syndrome or Laugier-Hunziker Syndrome. Therefore, early identification of polyps is crucial, as they may increase the risk of neoplasia in areas outside the intestine. Dentists should be aware of various lesions that can aid in diagnosis in addition to oral symptoms to ensure patients receive an appropriate treatment plan.

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CONFLICT OF INTEREST

The authors declare no competing interests.

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