International Journal of Research in Dermatology
Zahrani AK et al. Int J Res Dermatol. 2025 May;11(3):257-262
http://www.ijord.com

DOI: https://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20251050

Case Report

Liraglutide-induced oral hyperpigmentation: a case report and review of management strategies

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Received: 11 April 2025
Accepted: 22 April 2025

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ABSTRACT

A 41-year-old female patient with no significant past medical history presented with asymptomatic hyperpigmentation of the oral mucosal surfaces, noticed over two months. The onset of hyperpigmentation coincided with the use of Liraglutide injections for weight §mg. The patient was also taking ferrous sulfate supplements for the past two months without prior adverse effects. Physical examination revealed multiple hyperpigmented macules on the bilateral buccal mucosa, lower gingiva, lower alveolar mucosa, and anterior tongue, along with mild lip hyperpigmentation. Laboratory tests, including thyroid function and serology, were normal. Histopathological examination showed chronic interface mucositis. The patient was treated with topical tacrolimus 0.03% cream, applied once daily, resulting in significant improvement within one week. This case suggests a possible link between Liraglutide and oral hyperpigmentation, highlighting the importance of considering medication-induced etiologies in such presentations. Additionally, using lip balm with SPF is recommended to prevent further pigmentation.

Keywords: Oral hyperpigmentation, Asymptomatic hyperpigmentation, SPF

INTRODUCTION

Oral hyperpigmentation is a condition characterized by darkened patches or spots within the oral cavity, resulting from an abnormal increase in melanin or other pigments in the oral mucosa.[1] This condition can stem from various factors, including genetic predisposition, systemic diseases, and environmental influences such as tobacco use. However, medication-induced hyperpigmentation, although relatively rare, is a clinically significant phenomenon.[2]

Liraglutide, marketed under the brand name Saxenda, is a glucagon-like peptide-1 (GLP-1) receptor agonist widely prescribed for managing obesity and type 2 diabetes mellitus. It functions by enhancing glucose-dependent insulin secretion, inhibiting glucagon release, and slowing gastric emptying, thereby promoting satiety and weight loss.[3-5] While Liraglutide is generally well-tolerated, common side effects primarily include gastrointestinal symptoms such as nausea, vomiting, and diarrhea.[6] The emergence of oral hyperpigmentation as an adverse effect, however, has not been widely reported, making this case particularly noteworthy.[7]

Hyperpigmentation of the oral mucosa can arise from several etiologies, including physiological processes, pathological conditions, and external influences. Physiological pigmentation is commonly observed in individuals with darker skin tones and is usually uniform and symmetrical.[8,9] Pathological pigmentation, on the other hand, can present as focal, asymmetrical patches that may necessitate further investigation. Drug-induced hyperpigmentation is an important consideration, particularly in patients with recent changes in medication. The pathogenesis of drug-induced hyperpigmentation

often involves the medication's impact on melanogenesis, the process by which melanin is produced by melanocytes.[10,11] Certain drugs can stimulate melanocyte activity or increase melanin production through various mechanisms, including direct cytotoxic effects, stimulation of melanocyte-stimulating hormones, or inflammatory responses that indirectly enhance melanogenesis.[12-14] Medications known to cause hyperpigmentation include antimalarials, cytotoxic drugs, antibiotics, and psychotropic agents. However, there is limited literature on the association between GLP-1 receptor agonists, such as liraglutide, and hyperpigmentation.[16]

Liraglutide's primary mechanism of action is through the activation of the GLP-1 receptor, which is expressed in various tissues, including the pancreas, gastrointestinal tract, and central nervous system.[17] While the exact mechanism by which Liraglutide may induce hyperpigmentation remains unclear, it is hypothesized that the drug's systemic effects could potentially influence melanocyte activity either directly or indirectly.[18,19] Additionally, individual variations in drug metabolism and genetic predisposition may contribute to the development of this rare side effect.[20] In the context of Liraglutide-induced hyperpigmentation, the existing literature provides minimal insight into this phenomenon.[21]

A comprehensive review of case reports and clinical trials reveals that most documented side effects of Liraglutide are gastrointestinal in nature, with few reports addressing dermatological or mucosal changes.[9,22,24] This gap in the literature underscores the need for further research to elucidate the mechanisms and risk factors associated with Liraglutide-induced hyperpigmentation.

The clinical presentation of oral hyperpigmentation can vary, but medication-induced cases are often distinguished by their asymptomatic nature, with no associated pain, swelling, or ulceration. This contrasts with other causes of oral mucosal changes, such as inflammatory or infectious conditions, which are typically accompanied by additional symptoms.[25]

The absence of systemic symptoms in drug-induced hyperpigmentation further supports the likelihood of a localized drug effect rather than a manifestation of an underlying systemic disease.[26] This case report documents a unique presentation of oral hyperpigmentation induced by Liraglutide (Saxenda) in a 41-year-old female patient, who had no significant past medical history.

CASE REPORT

A 41-year-old female patient, with no significant past medical history, presented with asymptomatic hyperpigmentation of the oral mucosal surfaces. She had observed these changes for approximately two months before seeking medical advice. The hyperpigmentation was not preceded by erythema. The patient had been receiving Liraglutide injections for weight loss, with a gradual dose escalation over six months. The dosing regimen started at 0.5 mg, increased to 1.2 mg, and subsequently reached 1.8 mg. Concurrently, she had been taking ferrous sulfate supplements for the past two months, having previously taken the same supplements two years ago without any noticeable side effects. The patient had also undergone lip filler injections twice, with the last procedure completed about three years ago, both of which were uneventful.

A comprehensive review of systems was unremarkable. The patient denied using other medications in recent years, introducing new cosmetic products, or experiencing pruritus associated with any topical agents. There were no other skin or mucosal lesions, and no involvement of the scalp or nails.

The patient reported no significant family history. She is a non-smoker and reported no other notable social history factors. Vital signs were stable. Oral examination revealed multiple hyperpigmented macules over the bilateral buccal mucosa, lower gingiva, lower alveolar mucosa, and a few on the anterior tongue. Generalized mild hyperpigmentation was also observed on the lips. No other mucosal or skin involvement was noted.

All laboratory tests were within normal limits, including thyroid function tests and serology. A biopsy was performed, revealing chronic interface mucositis. The histopathology image from the first visit (Figure 1) illustrates these findings. The patient was prescribed topical tacrolimus 0.03% cream, applied once daily. After one week of treatment, the patient reported significant improvement. The follow-up image (Figure 2), taken one week after initiating tacrolimus therapy, shows a marked reduction in hyperpigmentation.

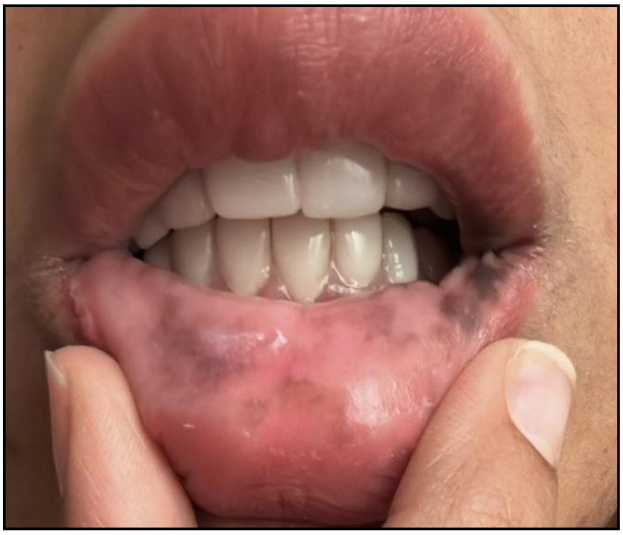

Figure 1: First visit showing hyperpigmentation on lips and oral mucosa.

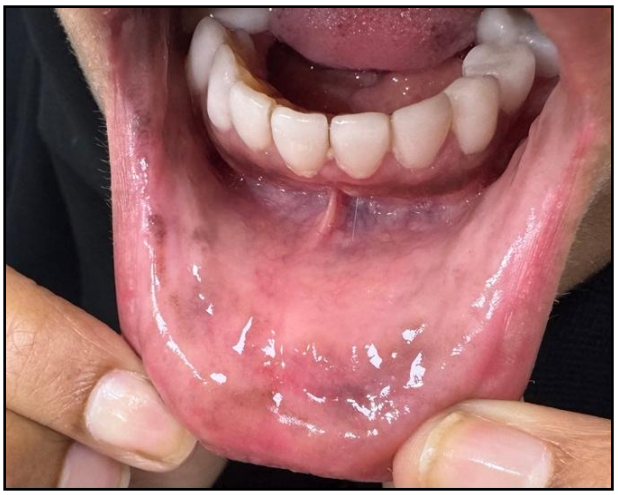

Figure 2: Image taken one week after using tacrolimus, showing significant improvement in oral hyperpigmentation.

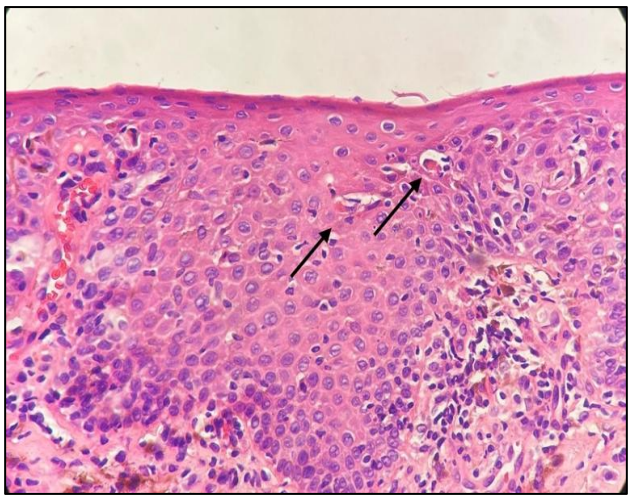

Figure 3: Histopathological image of in oral hyperpigmentation.

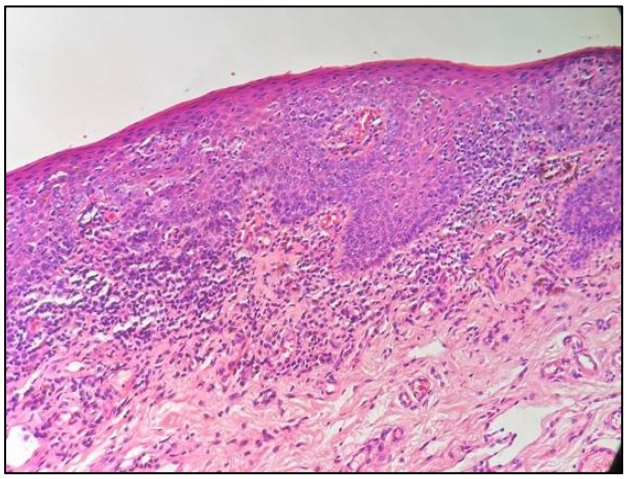

Figure 4: Histopathological image of improvement in oral hyperpigmentation.

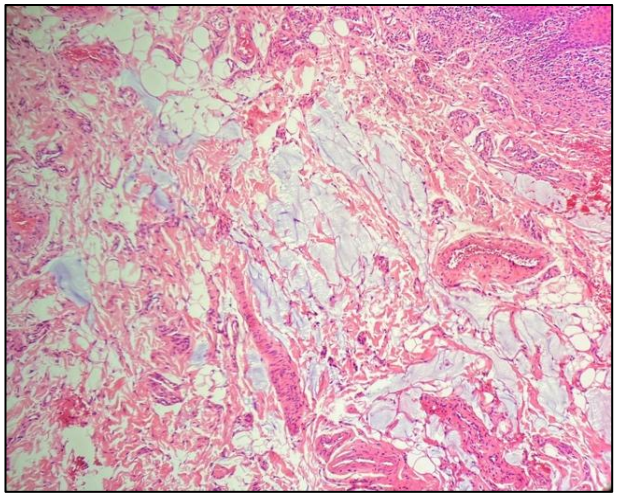

Figure 4: Histopathological image of an reduction in hyperpigmentation.

DISCUSSION

The differential diagnosis for oral hyperpigmentation is broad, encompassing physiological pigmentation, medications, systemic diseases, and neoplasms. In this case, several factors point towards a drug-induced etiology. Firstly, the hyperpigmentation developed gradually over two months, coinciding with the initiation and dose escalation of liraglutide. Secondly, the hyperpigmentation presented as multiple macules without erythema, a pattern often observed with drug-induced pigmentation.

Lastly, the patient's medical history, review of systems, and normal laboratory investigations ruled out other likely causes, such as systemic diseases or nutritional deficiencies. Liraglutide, a glucagon-like peptide-1 receptor agonist, is primarily used for type 2 diabetes management and weight loss.[4] While generally well-tolerated, GLP-1 receptor agonists have been associated with various side effects, including gastrointestinal disturbances, pancreatitis, and skin reactions.[27]

Although not frequently reported, drug-induced pigmentation is a known side effect of GLP-1 receptor agonists. The exact mechanism of GLP-1 receptor agonist-induced pigmentation remains unclear. However, it is postulated that these medications may stimulate melanocytes, the cells responsible for melanin production, leading to increased pigmentation.[28] The histopathological findings of chronic interface mucositis further support a drug-induced reaction.

Interface mucositis is characterized by inflammation at the junction of the epithelium and connective tissue, a common finding in drug-induced eruptions. Other potential causes of the patient's hyperpigmentation, such as ferrous sulfate supplementation and lip fillers, were considered less likely. The patient had previously taken ferrous sulfate without experiencing similar side effects.

Additionally, the lip filler injections were performed three years prior to the onset of hyperpigmentation, making a delayed reaction unlikely.

The management of drug-induced hyperpigmentation primarily involves identifying and discontinuing the causative agent, if possible.[29] However, in this case, liraglutide was prescribed for weight loss, and discontinuation might not be ideal without exploring alternative weight management strategies with the patient. Tacrolimus is effective in treating various inflammatory dermatoses, including drug-induced reactions.[30] The patient's significant improvement after one week of tacrolimus treatment further supports the diagnosis of drug-induced hyperpigmentation. Continued monitoring and potential discontinuation of liraglutide should be considered, especially if the pigmentation resolves with topical treatment.

Therefore, a two-pronged approach was adopted. Tacrolimus ointment inhibits T-lymphocyte activation, reducing inflammation and suppressing the immune response. It is considered a first-line treatment for various inflammatory skin conditions, including drug-induced pigmentation.[32] While its use in oral mucosa is considered off-label, studies have shown its efficacy and safety in treating oral lichen planus and other inflammatory oral conditions.[33,34] The patient's significant improvement after one week of treatment with topical tacrolimus 0.03% cream supports its effectiveness in this case.

Continuous monitoring of the pigmentation is crucial. If the pigmentation resolves completely with topical tacrolimus and does not recur, it strengthens the suspicion of liraglutide as the causative agent. In such a scenario, discontinuing liraglutide should be considered, weighing the benefits of weight management against the risk of pigmentation recurrence. While no large-scale studies specifically address liraglutide-induced oral hyperpigmentation and its management, some of the studies supports the chosen approach.

Krause provides a systematic review of drug-induced hyperpigmentation, highlighting its varied presentations and the importance of considering medications as a potential cause.[35] Some case reports and smaller studies have documented skin reactions, including pigmentation changes, associated with GLP-1 receptor agonists.[36-38] Topical corticosteroids, such as clobetasol propionate, could be considered as an alternative to tacrolimus, especially for short-term use.[39] However, they carry a higher risk of side effects like skin atrophy and telangiectasias.

While the role of UV radiation in drug-induced oral pigmentation is not fully established, advising patients on photoprotection measures like using lip balm with sun protection factor (SPF) is prudent. This measure can help shield the lips and surrounding areas from UV radiation, which may exacerbate pigmentation changes.[40] Long-term follow-up is essential to monitor for pigmentation resolution and recurrence. If the pigmentation persists despite treatment or recurs after liraglutide discontinuation, further investigation with a repeat biopsy or oral medicine specialist might be necessary.

CONCLUSION

This case report highlights a rare instance of oral hyperpigmentation induced by Liraglutide in a 41-year-old female with no significant past medical history. The hyperpigmentation developed after six months of Liraglutide use and was not associated with other systemic symptoms. Histopathological findings indicated chronic interface mucositis, and the patient responded well to topical tacrolimus 0.03% cream within one week. While oral hyperpigmentation is a well-recognized condition with multiple etiologies, the association with Liraglutide therapy is novel and warrants further investigation.

This case underscores the need for clinicians to consider drug-induced causes of mucosal pigmentation, particularly with Liraglutide therapy. Recognizing medication-induced hyperpigmentation as a potential adverse effect of Liraglutide is crucial for accurate diagnosis and management. Protective measures, such as using lip balm with SPF, can help prevent further pigmentation. This case report contributes to the growing body of literature on the diverse side effect profile of GLP-1 receptor agonists and highlights the importance of thorough patient evaluation and monitoring during pharmacotherapy. Further research is needed to understand the mechanisms behind this rare side effect and to identify risk factors for its development.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Zahrani AK, Basendwh MA, Alzaidi RS, Aldraibi SM, Abualola AH. Liraglutide-induced oral hyperpigmentation: a case report and review of management strategies. Int J Res Dermatol 2025;11:257-62.