

Reviewer #1:

Specific Comments to Authors:

1 Title. Does the title reflect the main subject/hypothesis of the manuscript?

Reviewer: A case report is not the proper design to establish causality. You need to change the title.

The title has been changed to “**Habitual khat chewing and Oral Melanoacanthoma: A case report**”

2 Abstract. Does the abstract summarize and reflect the work described in the manuscript? Reviewer: No.

The background section needs to elaborate on oral melanoacanthoma, and indicate the aim of this case report. Done

BACKGROUND

Habitual khat (*Catha edulis*) chewing has been proven to cause numerous oral tissue changes. However, oral melanoacanthoma triggered by chronic khat chewing is rare. Oral melanoacanthoma is an uncommon, sudden, asymptomatic, benign pigmentation of the oral cavity. Under the microscope, the epithelial layer of the oral mucosa showed dendritic melanocyte proliferation and acanthosis. The study aimed to highlight chronic khat chewing as a trigger for oral melanoacanthoma.

There is no methodological section in the abstract.

Answer: Following the journal's guidelines and based on the journal's requirements, there is no methodological section in the abstract of the case report.

The case summary does not include the histopathological findings, which is, in my opinion, the most important finding of this case report.

Answer: (Added)

In this case, the definitive diagnosis was oral melanoacanthoma. This diagnosis was made based on the patient's history, clinical lesion presentation, and microscopic biopsy results.

The conclusion seems to indicate causality, but a case report is not the proper design for establishing causality.

Furthermore, the diffuse statement that “oral melanoacanthoma should be considered in the differential diagnosis of diffused brownish-black oral-pigmented lesions” is out of focus.

Answer:

~~(deleted)Therefore, oral melanoacanthomas should be considered in the differential diagnosis of diffused brownish black oral pigmented lesions.~~

The conclusion should answer the question: What is the aim of this case report? **Done**

Answer: (Added)

The study aimed to highlight chronic khat chewing as a trigger for oral melanoacanthoma.

3 Key words. Do the key words reflect the focus of the manuscript?

Reviewer: **Yes.** “Oral melanoacanthoma” and “Khat chewing” are probably not needed as it is already in the title. “oral lesions” is suggested as a relevant key word.

Answer:

“Oral lesions” was added and “Khat chewing” was deleted as suggested by the reviewer.

4 Background. Does the manuscript adequately describe the background, present status and significance of the study?

No. There is a lack on describing khat (*Catha edulis*) and the association to oral lesions and periodontal disease. **Done**

Answer:

Habitual khat (*Catha edulis*) is commonly found in a few parts of Africa and many countries in the Middle East, such as the Arabian Peninsula. In some cultures, it has been associated with social customs. Recently, with global migration, khat chewing habits have reached the USA, Europe, and Australia^[1,2]. Khat chewing is customarily practiced at prolonged social gatherings called khat sessions, lasting several hours each day. The custom usually entails inserting and chewing fresh khat leaves to form a bolus that is held in the lower buccal vestibule against the cheek on one side or, in

rare cases, on both sides. At the end of the session, the quid is expelled, while the juice is partially expectorated and absorbed^[3, 4].

Fresh khat leaves have psychoactive, sympathomimetic, and euphoric effects caused by a principal alkaloid known as cathinone, which is structurally similar to amphetamine. Khat users chew fresh or dried leaves and buds^[5,6].

The description of oral melanoacanthoma is also rudimentary (basic/essential) –

Answer:

Oral melanoacanthoma is an uncommon, sudden, asymptomatic, benign pigmentation of the oral cavity. It typically occurs suddenly and is clinically characterized by diffused, rapidly growing, dark brown to black colored, and macular tissue pigmentation. It commonly affects the buccal mucosa (51.4%), the palate and lips (22–15%), and the gingiva (>6%)^[10]. African Americans and younger patients are more likely to develop oral melanoacanthoma^[11]. Histopathological analysis has revealed dendritic melanocyte dispersion and acanthosis of the superficial epithelium^[12].

What are the complications? Done

What are the underlying known aetiologies and risk factors? This is somewhat introduced in the Discussion section of the paper but missing in the Background section. Done

Many studies have shown that chewing fresh khat leaves causes mood swings, depression, insomnia, hypertension, ischemic heart disease, anorexia, and constipation. Khat is not associated with addiction, but may lead to psychosomatic dependence^[7].

Chewing khat causes several potentially harmful systemic health effects, including renal toxicity, gastrointestinal and liver problems, and cardiovascular abnormalities. In addition, long-term khat consumption has been linked to several oral and dental conditions, including keratotic white lesions, mucosal pigmentation, plasma cell

stomatitis, teeth attrition and loss, discoloration, temporomandibular joint issues, gingival recession, and periodontal infections^[8].

In animals, khat increase the free radicals that cause tissue damage. Thus, high doses of the active ingredient of khat are released into the oral fluids and most of it is absorbed into the oral tissues^[9].

Oral melanoacanthoma is self-limiting in nature and is secondary to tissue trauma, which stimulates melanocytic activity. It disappears after eliminating irritants or biopsy. This strengthens the reactive nature of the lesions^[13].

The Clinical differential diagnosis of oral pigmentation includes several topical and systemic causes.

This section should also state the aim of this case report and present the significance of the study. Done

This study aimed to highlight chronic khat chewing as a trigger for oral melanoacanthoma.

It seems like the authors are mixing tobacco and khat. Khat (*Catha edulis*) is not a sort of tobacco. But smoking habits and the use of shisha or chewing tobacco are relevant and should be investigated further. Done

5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail?

Reviewer: In a case report there is usually no need of a meticulous description of the methods used. The histopathological description is well described.

6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field?

There is a lack of clinical information on symptomatology,

Answer: (added)

History of present illness

The patient had a 4-month history of **asymptomatic**, unilateral diffuse brown oral pigmentation that appeared abruptly and diffused rapidly.

There is a lack of clinical information on medical history and exposure data

Answer: (added)

Chief complaints

A 26-year-old **healthy** male Saudi individual with a khat chewing habit of **approximately 100 g of khat/2 sessions daily for more than 12 years** visited the oral medicine clinic at Dental Hospital, King Saud University, for the examination of oral brown pigmentations.

There is a lack of clinical information on dental/periodontal assessment.

Answer: (added)

Intraoral examination:

On intraoral examination, the patient had full dentition and no clinical dental caries; however, he had poor oral hygiene, tooth discoloration, and a yellowish tongue.

Did the lesion hurt? Any buccal bleeding? Why did the patient come to the clinic?

Answer: (added)

- The patient had a 4-month history of **asymptomatic lesions**.

- No bleeding was noticed.

- This was stated in the first paragraph of the case summary section. "for the examination of oral brown pigmentations."

Routine follow-up? Any weight loss, night sweats, fatigue?

Answer: (added)

History of present illness

“Oral pigmentation was not associated with weight loss, fatigue, or night sweats in this study. The patient reported that he had undergone routine dental follow-up.”

How much khat did he chew per day/session)?

Answer: (added)

Chief complaints

A 26-year-old healthy male Saudi individual with a khat chewing habit of approximately 100 g of khat/2 sessions daily for more than 12 years.

Any other substances used whilst chewing khat (drinking soft drinks, use of shisha)?

Any other exposures – chewing tobacco, shisha, smoking, betel nut, heavy metals etc.?

Answer: (added)

History of present illness

“The patient had no history of drinking soft drinks, chewing tobacco or shisha, smoking, consuming betel nuts, or heavy metal exposure.”

Other relevant clinical assessments are known related to khat – blood pressure, weight/BMI, skin rash, ascites, jaundice – which might strengthen the link to khat use?

Answer: (added)

Physical examination

Physical and systemic examination:

Physical examination revealed no remarkable skin rash, ascites, jaundice, or any other abnormal findings. The patient had a slightly elevated blood pressure of 122/79 mmHg, a height of 167 cm, and a weight of 75 kg.

Although I am not a dentist, I am missing information from the intraoral examination: What is the dental status? Tongue status?

Answer: (added)

Intraoral examination:

On intraoral examination, the patient had full dentition and no clinical dental caries; however, he had poor oral hygiene, tooth discoloration, and a yellowish tongue.

Other oral lesions – negative findings are also of interest as khat chewing is associated with leukoplakia, stomatitis, xerostomia, periodontal disease, tooth loss and keratotic white lesions.

Answer: (added)

Intraoral examination:

“The oral cavity showed no signs of leukoplakia, stomatitis, xerostomia, periodontal disease, or keratotic white lesions.”

Laboratory investigations should also include basic biochemistry, including renal and liver status.

Answer: (added)

Laboratory examinations

The blood results were within normal limit; a white blood cell count of $9.7 \times 10^3 / \mu\text{L}$; a red blood cell count of $5.1 \times 10^6 / \mu\text{L}$; a platelet count of $319 \times 10^3 / \mu\text{L}$; a hemoglobin count of 14.2 g/dL; cortisol 21 mcg/dL; ACTH 9.1 pmol/L; a BUN value of 24 mg/dL; serum creatinine value of 0.97 mg/dL; potassium, 4.6 mmol/L; sodium, 137 mmol/L; albumin, 49 g/L; total bilirubin of 18 $\mu\text{mol/L}$; alanine aminotransferase, 48 IU/L; aspartate aminotransferase, 52 IU/L; and alkaline phosphatase, 294 IU/L.

Imaging examination is indeed applicable but not performed in this case, and that is acceptable. Okay

It was not clear if the histopathological findings did indicate any malignant features. That said, the histopathological findings are of high interest and the most important finding in this case report.

Answer:

Added: with no features of malignancy

7 Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently?

Reviewer: As mentioned previously, the discussion section provides information that belongs to the Background section (see comments above). Done

It is a very strong statement to claim that this study has been "(...) eliminating all other possible causative factors. (...)", although the authors are more modest when saying that "(...) khat could have triggered the oral melanoacanthoma in the current case. (emphasis added) (...). However, the authors claim later in the discussion that "(...) the causative agent was eliminated (...)", and again that is too strong statement as they can not be sure about that from this case report.

The discussion section does not reflect the limitation of a case report not being an adequate design for establishing causality. In fact, the discussion section does not reflect on any limitations of this study at all.

The sentence was emphasized

The conclusion is therefore too strong and inadequate claiming khat as the cause to the oral melanoacanthoma found in this patient.

Moreover, the authors are again blurring the picture by mixing tobacco use and chewing khat.

Chewing tobacco was deleted from the sentence.

Furthermore, the authors bring in oral cancer (for the first time!) in the conclusion, and it is unclear if this is linked to khat use or tobacco use.

The sentence was deleted.

Lastly, the author does not discuss the scientific significance of this case report or the need for further studies.

Done

8 Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends?

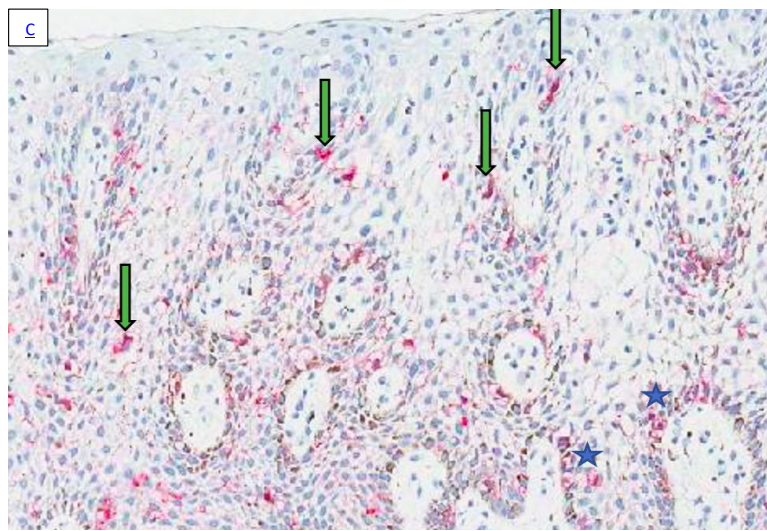
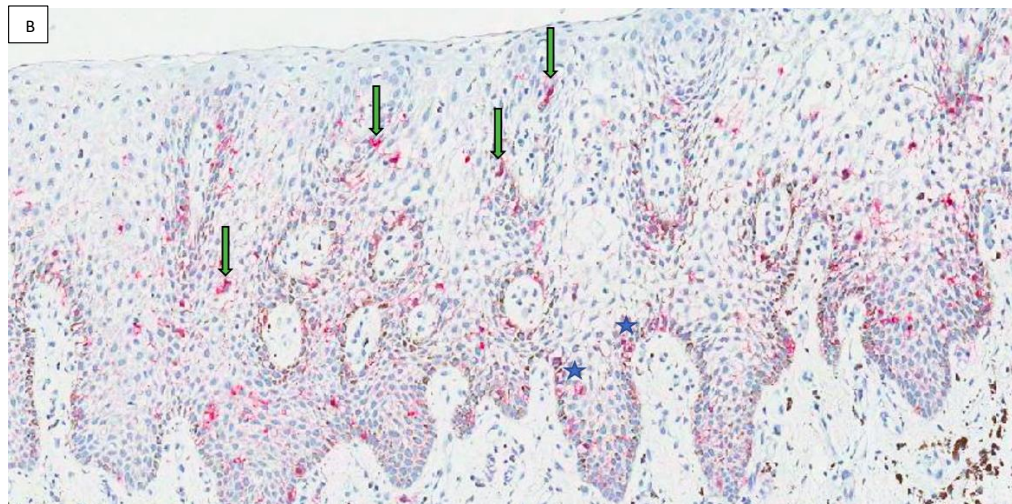
Reviewer:

Figure 1B – buccal mucosa is blurred/out of focus.

The blurred part of this picture was cropped.



Figure 2 – a higher magnitude would be preferred. And also add arrows/ markings showing the melanocytic hyperplasia, and the dendritic melanocytes.



B and C: Histopathological photomicrograph of Melan-A-stained section show dendritic melanocytes (green arrows) and melanocytic hyperplasia (blue stars) throughout the epithelium.

Figure 3 – there should be a consistency in the use of pictures in order to compare the clinical findings during follow up. In these pictures we see areas of mucosal discoloration not displayed in previous pictures, and therefore difficult to interpret if there has been any improvement?

Answer:

One picture was deleted

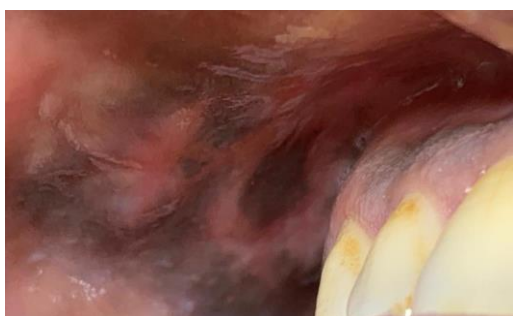


Figure 3 Follow-up clinical photos. A: 2-month follow-up clinical photos of the right buccal mucosa showing partial resolution of the oral lesion. B: A 4-month follow-up clinical photo of the oral cavity illustrates the complete resolution of the oral melanoacanthoma.

9 Biostatistics. Does the manuscript meet the requirements of biostatistics?

Reviewer: NA

10 Units. Does the manuscript meet the requirements of use of SI units?

Reviewer: Yes

11 References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references?

Reviewer: The reference works of Al-Maweri SA and Kalakonda B as mentioned previously (see comments above).

Answer:

The references on khat are ancient and should be updated. The references were updated.

1. **Kassim S**, Jawad M, Croucher R, Akl EA. The Epidemiology of Tobacco Use among Khat Users: A Systematic Review. *Biomed Res Int*.2015;313692. [PMID: 26273606 DOI: 10.1155/2015/313692]
2. **Awadalla NJ**, Suwaydi HA. Prevalence, determinants and impacts of khat chewing among professional drivers in Southwestern Saudi Arabia. *East Mediterr Heal J*. 2017 May;23(3):189–97. [PMID: 28493266 DOI: 10.26719/2017.23.3.189]
3. **Al-Sharabi AK**, Shuga-Aldin H, Ghandour I, Al-Hebshi NN. Qat chewing as an independent risk factor for periodontitis: a cross-sectional study. *Int J Dent*.2013;317640. [PMID: 23509461 DOI: 10.1155/2013/317640]
4. **Al-Maweri SA**, Alaizari NA, Al-Sufyani GA. Oral mucosal lesions and their association with tobacco use and qat chewing among Yemeni dental patients. *J Clin Exp Dent*. 2014;6(5):e460-6. [PMID: 25674309 DOI: 10.4317/jced.51706]
5. **Al-Hebshi NN**, Skaug N. Khat (*Catha edulis*)-an updated review. *Addict Biol*. 2005;10(4):299–307. [PMID: 16318950 DOI: 10.1080/13556210500353020]
6. **Hijazi M**, Jentsch H, Al-Sanabani J, Tawfik M, Remmerbach TW. Clinical and cytological study of the oral mucosa of smoking and non-smoking qat chewers in Yemen. *Clin Oral Investig*. 2016;20(4):771–9. [PMID: 26319978 DOI:

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10.1007/s00784-015-1569-2]

7. **Ageely HMA**. Health and socio-economic hazards associated with khat consumption. *J Family Community Med*. 2008 Jan;15(1):3–11. [PMID: 23012161]
8. **Al-maweri SA**, Warnakulasuriya S, Samran A. Khat (*Catha edulis*) and its oral health effects : An updated review. *J Investig Clin Dent*. 2018; 9(1). [PMID: 28834423 DOI: 10.1111/jicd.12288]
9. **Al-Kholani AI**. Influence of Khat Chewing on Periodontal Tissues and Oral Hygiene Status among Yemenis. *Dent Res J (Isfahan)*. 2010;7(1):1–6. [PMID: 21448439]
10. **Galindo-Moreno P**, Padial-Molina M, Gómez-Morales M, Aneiros-Fernández J, Mesa F, O'Valle F. Multifocal oral melanoacanthoma and melanotic macula in a patient after dental implant surgery. *J Am Dent Assoc*. 2011 Jul;142(7):817–24. [PMID: 21719804 DOI: 10.14219/jada.archive.2011.0270]
11. **Tapia JL**, Quezada D, Gaitan L, Hernandez JC, Paez C, Aguirre A. Gingival melanoacanthoma: case report and discussion of its clinical relevance. *Quintessence Int*. 2011;42(3):253–8. [PMID: 21465013]
12. **Cantudo-Sanagustín E**, Gutiérrez-Corrales A, Vigo-Martínez M, Serrera-Figallo M ángeles, Torres-Lagares D, Gutiérrez-Pérez JL. Pathogenesis and clinicohistopathological characteristics of melanoacanthoma: A systematic review. *J Clin Exp Dent*. 2016;8(3):e327–36. [PMID: 27398186 DOI: 10.4317/jced.52860]
13. **Gondak R-O**, da Silva-Jorge R, Jorge J, Lopes M-A, Vargas P-A. Oral pigmented lesions: Clinicopathologic features and review of the literature. *Med Oral Patol Oral Cir Bucal*. 2012;17(6):e919-24. [PMID: 22549672 DOI: 10.4317/medoral.17679]
14. **Agha RA**, Borrelli MR, Farwana R, Koshy K, Fowler AJ, Orgill DP, et al. The SCARE 2018 statement: Updating consensus Surgical CAse REport (SCARE)

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guidelines. *Int J Surg*. 2018;60:132–6. [30342279 DOI:10.1016/j.ijssu.2018.10.028]

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15. **Feller L**, Masilana A, Khammissa RAG, Altini M, Jadwat Y, Lemmer J. Melanin: the biophysiology of oral melanocytes and physiological oral pigmentation. *Head Face Med*. 2014;10:8. [PMID: 24661309 DOI: 10.1186/1746-160X-10-8]
16. **Andrews BT**, Trask DK. Oral melanoacanthoma: A case report, a review of the literature, and a new treatment option. *Ann Otol Rhinol Laryngol*. 2005;114(9):677–80. [PMID: 16240929 DOI: 10.1177/000348940511400904]
17. **Brooks JK**, Sindler AJ, Scheper MA. Oral Melanoacanthoma in an Adolescent. *Pediatr Dermatol*. 2010;27(4):384–7. [PMID: 20653859 DOI: 10.1111/j.1525-1470.2010.01177.x]
18. **Tomich CE**, Zunt SL. Melanoacanthosis (Melanoacanthoma) of the Oral Mucosa. *J Dermatol Surg Oncol*. 1990;16(3):231–6. [PMID: 2179347 DOI: 10.1111/j.1524-4725.1990.tb03958.x]
19. **Neville BW**, Damm DD, Allen CW BJ. Oral and Maxillofacial Pathology, 3rd Edition. 2008. 540 p.
20. **Fornatora ML**, Reich RF, Haber S, Solomon F, Freedman PD. Oral melanoacanthoma: a report of 10 cases, review of the literature, and immunohistochemical analysis for HMB-45 reactivity. *Am J Dermatopathol*. 2003;25(1):12–5. [PMID: 12544093 DOI: 10.1097/00000372-200302000-00003]
21. **Carlos-Bregni R**, Contreras E, Netto AC, Mosqueda-Taylor A, Vargas PA, Jorge J, et al. Oral melanoacanthoma and oral melanotic macule: A report of 8 cases, review of the literature, and immunohistochemical analysis. *Med Oral Patol Oral Cir Bucal*. 2007;12(5):374–9. [PMID: 17767102]

12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate?

Reviewer: As mentioned previously, the abstract has some deficiencies and there is a need of re-structuring information in the Background / Discussion section. There is a minor need for language polishing.

13 Research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting?

Reviewer: Yes, but with several deficiencies as mentioned above.

14 Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics?

Reviewer: Yes

Reviewer #2:

Specific Comments to Authors: In this manuscript, the authors stated that oral melanoacanthoma caused by chronic khat chewing is rare, and chewing khat is an extrinsic factor that can cause oral pigmentation. So, if the authors could provide more internal mechanism that will much better explain the causal relationship between the oral melanoacanthoma and habitual khat chewing.

Answer: (Added)

Oral lesions induced by chronic chewing of khat in the oral mucosa present with brown discoloration due to increased epithelial melanin deposition.

In animals, khat hampers the body's ability to clear free radicals. Consequently, free radicals can cause tissue damage. Chronic khat chewers generally keep the khat bolus in the oral vestibule for hours. Therefore, high doses of the active ingredient of

khat, “alkaloid cathinone,” are released into the oral fluids and most of it is absorbed into the oral tissues^[9].

Melanin production increases in areas of irritation that cause pigmented lesions. Melanin protects against environmental stressors such as ultraviolet radiation and reactive oxygen species. The purpose of increased melanocyte proliferation and production of melanin in the epithelium is to protect and produce a balanced microenvironment that contributes to tissue homeostasis^[15].