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Oral Manifestations of Chloroquine and Hydroxychloroquine: Differential Diagnoses

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Abstract

Chloroquine phosphate and hydroxychloroquine sulfate are organic compounds, known as aminoquinolines for containing an amino group attached to a quinoline ring. They have been used since World War II as antimalarial agents. The article search that made up this review was carried out in the PubMed database, using the keywords "Chloroquine", "Hydroxychloroquine", and "Oral Manifestations", in the period including 2005 to 2020. The sample size was 7 female patients aged 40 to 66 years, with an age predominance of between 50 and 60 years old. The predominant lesion site was the hard palate with 6 cases. To reach the diagnosis of pigmented lesions in the oral cavity, meticulous anamnesis prior to physical examination is extremely important. In this pandemic and post-pandemic period, a more detailed investigation of the medications used by the patient in recent periods, such as chloroquine and hydroxychloroquine are essential to detect if the lesion was possibly caused by these drugs.

Keywords

Hydroxychloroquine, Chloroquine, Oral Manifestations, Hyperpigmentation, COVID-19

1. Introduction

Chloroquine phosphate and hydroxychloroquine sulfate are organic compounds, and known as aminoquinolines for containing an amino group attached to a quinoline ring. They have been used since World War II as antimalarial agents. Hydroxychloroquine sulfate is a derivative of chloroquine and was synthesized for the first time in 1946, by introducing a hydroxyl group [1] (Rainsford *et al.*

2015).

Both drugs share the same mechanism of action. The compounds are fully and rapidly absorbed after oral administration and are excreted by the kidney and liver. Both are soluble in water, but for having a hydroxyl group, hydroxychloroquine is more soluble. The half-life is approximately 1 - 2 months. The clinical safety profile of hydroxychloroquine is better than that of chloroquine and allows for higher daily doses with fewer concerns about drug interactions [2] (Gautret *et al.* 2020).

In addition, due to their immunosuppressive, anti-inflammatory, antithrombotic and metabolic actions, they have been widely and successfully used in the treatment of lupus erythematosus, rheumatoid arthritis, diabetes, cutaneous porphyria, HIV, fungal infections, immunological, dermatological, and infectious diseases, among others. Their antitumor properties stand out, which make these drugs an option in the treatment of various tumors associated with radio and chemotherapy. They also cross the blood-brain barrier, which makes them attractive as a therapeutic resource in neurological diseases [3] (Plantone *et al.* 2018).

Systemic administration of these drugs over a long period, can lead to multifocal hyperpigmentation on the skin and mucosa. Their cutaneous side effects include mild skin reactions, such as alopecia, itching, angioedema, rashes and pigmentation changes, and they are also known to exacerbate skin conditions such as psoriasis and porphyria. Cardiac and neuromuscular toxicities, together with retinopathy that can lead to blindness are also recognized as potential complications of their use [3] [4] (Plantone *et al.* 2018; Kalampalikis *et al.* 2012); as well as gastrointestinal manifestations, including nausea, vomiting and diarrhea. Furthermore, chloroquine or hydroxychloroquine overdose can cause acute intoxication and even death.

Of dental interest, oral hyperpigmentation induced by drug therapy can be attributed to stimulation of melanin production in melanocytes and/or tissue deposition of hemosiderin. Oral hyperpigmentation is reported mainly on the hard palate, but can be present in the gums, lips, and oral mucosa. It manifests as a well-defined pigmentation, brown, grayish blue or dark purple, in many sizes,being diffuse macular lesions with well-defined edges (**Figure 1**). The changes are usually reversible when medication is stopped or the dose is reduced, and treatment is not necessary. However, it is recommended that the patient be referred to their doctor, due to the risk of presenting other symptoms [4] [5] (Kalampalikis *et al.* 2012; de Filho *et al.* 2012).

Hyperpigmentation of the oral mucosa is common in melanoderm individuals (due to physiological deposition of melanin). Other conditions associated with hyperpigmentation of the oral mucosa include: melanocytic nevus, amalgam tattoo, and more rarely, melanoma; any of which can also present as an early sign of systemic disease. The dental surgeon must be aware of this context, in order to identify, treat, or otherwise avoid such effects whenever possible.

Figure 1. Hard palate hyperpigmentation—using chloroquine (ANDRADE *et al.* 2017).

Due to the greater toxicity that it presents in relation to hydroxychloroquine, most reports in the literature concerning oral manifestations due to the use of these drugs are related to chloroquine. Yet hydroxychloroquine also presents toxicity. Few cases of pigmentation attributed to chloroquine have been reported in the literature, and the incidence of hydroxychloroquine-induced pigmentation is estimated at between 7% and 13% [6] [7] (Sarma *et al.* 2020).

In December 2019, an outbreak of pneumonia began in Wuhan, China, spreading rapidly across the world. A new coronavirus (2019-nCoV) was identified, which is closely related to severe acute respiratory syndrome (SARS-CoV-2). The epidemic was declared a pandemic by the WHO on March 12, 2020. Faced with an urgent global pandemic, the scientific community looked to provide an effective treatment protocol for patients affected by COVID-19.

Among treatment options for COVID-19, chloroquine phosphate and hydroxychloroquine sulphate stand out. There is still much controversy about their efficacy and safety, which promotes great debate. Yet both chloroquine and hydroxychloroquine have been used in various treatment protocols and thousands of people have used these drugs. In view of this, the objective of this work is to evaluate side effects which can occur in the oral cavity due to the use of these drugs [8] [9] (Kleinegger *et al.* 2000).

2. Methodology

Thesearch for articles was carried out in the PubMed database, using the keywords "Chloroquine", "Hydroxychloroquine", and "Oral Manifestations", in the period including 2005 to 2020. The article selection process involved analysis of titles and abstracts, restricted on the English language. Using the comination strategy in the "Chloroquine and Oral Manifestations" and "Hydroxychloroquine and Oral Manifestations", "COVID-19 and Oral manifestations", "COVID-19 and hyperpigmentation". Preclinical studies (such as *in vitro* studies, animal studies, and literature reviews) were excluded, yieldinga selection of 53 articles. Studies not presenting oral manifestations involving hydroxychloroquine or chloroquine were excluded, finally resulting in 7 studies being accepted (**Figure 2**).

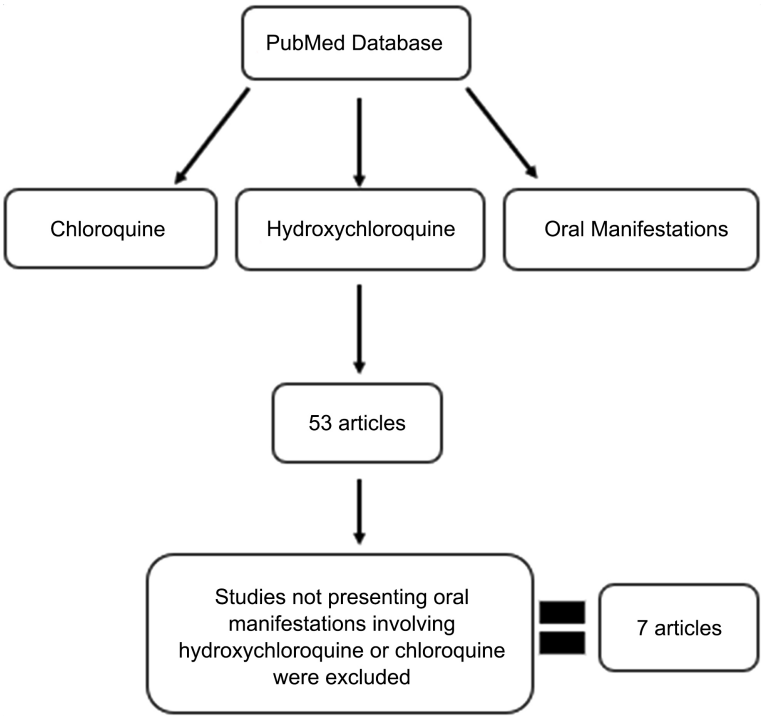

Figure 2. Literature search flow diagram.

3. Results

The results of the 7 studies are summarized in **Table 1**. The sample size was 7 female patients aged 40 to 66 years, with an age predominance of between 50 and 60 years old [4] [10] [11]. The predominant lesion site was the hard palate with 6 cases [5] [10] [11] [12] [13] [14] and 1 patient with an injury manifested in the mandibular gingival region [4]. The dosages ranged from 150 mg to 250 mg for chloroquine and from 200 mg to 400 mg for hydroxychloroquine. Chloroquine was the predominant drug reported [5] [11] [12] [13] [14]. The period of timeunder prescription for chloroquine ranged from 1 year to 15 years, and for hydroxychloroquine ranged from 8 months to 5 years. The predominant systemic disease, for which the use of the drug was justified, was rheumatoid arthritis [5] [10] [11] [12] [13] [14] with only one case related to Sjögren's syndrome [4]. Incisional biopsy for diagnostic confirmation of treatment was chosen in all cases. Interruption of the use of the medication [5] [10] [11] [12] followed. However, there were cases in which drug substitution [13] occurred and the injury was monitored [14].

4. Discussion

4.1. Oral Manifestations

When facing the injuries, we address in this study, the professional must adopt measures to optimize diagnosis and treatment. A detailed medical history with an accurate clinical examination is extremely important for elaboration of a diagnostic hypothesis. Due to the series of lesions presenting similar characteris-

tics and yet different causes, the dentist can use an incisional biopsy for diagnostic confirmation [12] (ANDRADE *et al.* 2017), consistently with the conduct of all authors of the studies in **Table 1** [4] [5] [10] [11] [12] [13] [14].

Another important aspect is managingthe use of these drugs, which needs to beperformed by the doctor (and patient) responsible for the treatment, analyzing the benefits and costs of using chloroquine and hydroxychloroquine in the medical treatment proposed. Thus, in some cases, it is possible to opt for a reduction in the usual dose or for atemporaryor definitive interruption altogether [12] (ANDRADE *et al.* 2017). The intensity of the effects and adverse reactions will dictate such maneuvers. It is worth mentioning that because the two drugs are in evidence in the current context of the pandemic of COVID-19, some protocols using these drugs are reporting using a higher dose than normally used for other diseases, leaving the question as to whether such doses can trigger earlier oral or even systemic manifestations in the patient. In the present study, we noted that the lowest dose was 150 mg of chloroquine during a period of 1 year [12] and the highest dose was 400 mg of hydroxychloroquine for 5 years [10]. As to time of use until an appearance of manifestations, we have that the period of 8 months [4] of hydroxychloroquine use and 15 years of chloroquine [5] use were the minimum and maximum times found in the studies in **Table 1**, revealing a great chronological variety in relation to the onset of hyperpigmentation in the oral cavity.

4.2. Isolated Small Black, Brown, Brownish Lesions

Pigmentations such as amalgam tattoo (**Figure 3**) and acquired melanocytic nevus (**Figure 4**), focal melanosis and oral melanoacanthoma are clinically smaller pigments that can be distinguished when taking a good medical history and performing exams. Small blackish pigments close to amalgam restorations are

Table 1. Studies presenting hydroxychloroquine and/or chloroquine oral manifestations.

Gender	Age	Site	Dose	Time of Use	Systemic Disease	Treatment
Feminine	64	Palate	200 mg/day Chloroquine	15 yrs.	Arterial hypertension and rheumatoid arthritis	Incisional biopsy
Feminine	55	Mandibular Gingiva	200 mg/day Hydroxychloroquine	8 months	Sjogren's syndrome	Incisional biopsy
Feminine	53	Palate	400 mg/day Hydroxychloroquine	5 yrs.	Arterial hypertension and rheumatoid arthritis	Incisional biopsy and discontinuation of medication
Feminine	40	Palate	250 mg/day Chloroquine	2 yrs.	Rheumatoid arthritis	Incisional biopsy—drug replacement with leflunomide 20 mg/day
Feminine	50	Palate	250 mg/day Chloroquine	4 yrs.	Rheumatoid arthritis	Incisional biopsy and discontinuation of medication
Feminine	66	Palate	250 mg/day Chloroquine	3 yrs.	Rheumatoid arthritis	Incisional biopsy and clinical follow-up
Feminine	60	Palate	150 mg/day Chloroquine	1 yr.	Rheumatoid arthritis	Incisional biopsy and discontinuation of medication

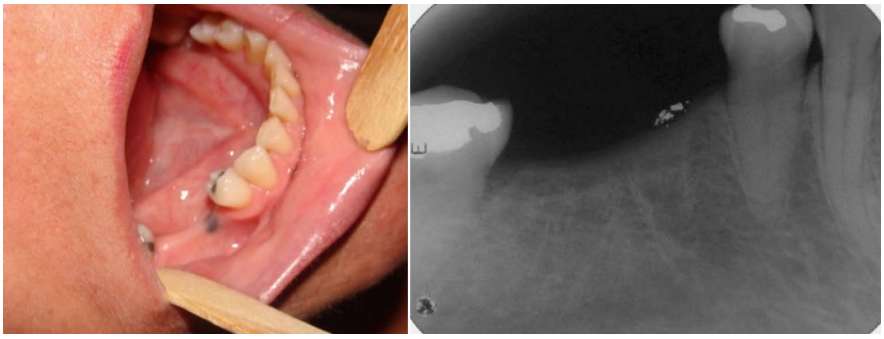

Figure 3. Amalgam tattoo, clinical and radiographic appearance (Stomatology clinic of UFC-Sobral).

Figure 4. Acquired melanocytic nevus (Stomatology clinic of UFC-Sobral).

believed to be caused by the metallic material itself, a relatively common finding in the oral mucosa. Usually, it occurs when fragments of the restoration loosen and are incorporated into the gums when rubbing floss on newly restored teeth, or even during the performance of the restoration itself [15]. It manifests as a bluish or black isolated macula of small dimensions that when submitted to radiographic examination reveals a radiopacity [16] (**Figure 3**).

The clinical history of the pigmentation is important, since, during extraction, part of the amalgam restoration can fracture and fall into the open socket. This can lead to future amalgam pigmentation without the presence of the causative tooth. Observing these characteristics, the lesion is radiographed and if presenting a radiopaque area compatible with the pigmented region, the diagnosis of amalgam pigmentation is concluded [15] (**Figure 3**). In case of an absence of radiopacity; additional tests must follow.

If there is only small, isolated pigmentation, (discarding amalgam pigmentation after radiography), other lesions are considered, one of which is an acquired melanocytic nevus which consists of an accumulation of melanin in the skin that also affects the mouth (**Figure 4**). Benign melanocytic nevi begin to develop in childhood and have an evolution period of up to 35 years, entering a period of involution afterwards. The pigmentation affects both sexes and is more prevalent in white individuals [15]. For differential diagnosis, the patient's age, time of evolution, and skin tone are considered, these, given that the lesion, which is

greater in childhood, presents slow and gradual growth which depends on racial differences [15], considering these and ruling out the hypothesis of possible malignant lesion, excisional biopsy is indicated for aesthetic purposes only.

The palate is a common site of pigmentation by chloroquine and hydroxychloroquine (**Figure 1**), and as seen in the Table1, the same is true for melanocytic nevus (**Figure 4**). Generally, nevus does not achieve large dimensions, unlike pigmentations by the medications in question. Itoccurs independently of any medication that the patient uses. A variant of the melanocytic nevus that draws attention is the blue nevus, which also consists of a benign proliferation of dermal melanocytes [15], yet these are in deeper layers of the skin, thus assuming a bluish tint that, when compared to pigmentation by anti-malarials, takes on a certain degree of distinction. Blue nevus is divided into two subtypes, common blue and cellular nevus, the distinction between them is in the size, where the first is smaller, varying in diameter between 1 to 5 mm; while the second can reach sizes of larger than 5 cm, which can resemble a chloroquine or hydroxychloroquine pigmentation (**Figure 1**), with prevalence in the palate, as is also the highest predilection for pigmentations caused by chloroquine and hydroxychloroquine (**Table 1**). Such lesions on the palate are a "warning light", and incisional biopsy is indicated. Depending on the histopathological result, treatment is determined. It is worth mentioning that there are controversies concerning potential risks of malignant transformation of blue nevus [17] [18].

Other dark and solitary pigments that can be found in the oral cavity are oral melanotic macula (focal melanosis) and oral melanoacanthoma (melanoacanthosis), which are acquired benign pigments. Both presentcharacteristics similar to pigmentation by the drugs in question, such as an oval or round macula, being asymptomatic, with brownish-yellow or dark brown color, and well-defined edges which stand out because they have a predilection for women, rapid proliferation. The involvement of melanoacanthosis that occurs almost exclusively in blacks with the focal melanosis presenting small dimensions [15]. Considering all of these clinical characteristics, and ruling out: a history of chronic smoking, patients with amalgam restoration, users of systemic medications with the potential for oral pigmentation, and those who do not have systemic disorders, it is the professional's responsibility to perform an excisional biopsy, or to periodically confirm the pigmentation, given its favorable prognosis. It is worth mentioning that due to the rapid and exaggerated growth of oral melanoacanthoma, incisional biopsy is indicated to rule out the possibility of melanoma [15].

4.3. Multiple Small Black, Brown, Brownish Lesions

4.3.1. Peutz-Jeghers Syndrome

This syndrome presents small dark brown-blue freckles, a few millimeters in diameter, occurring in the facial orifices, in the oral mucosa, and on the hands and feet. Pigmentation of the lips occurs more often (96% of cases), followed by pigmentation of the oral mucosa (83% of cases) [19]. Peri-ocular, pigmentation

is seen on the eyelids and along the eyelid margins, and, sometimes, on the eyelid conjunctiva [19], which differs from chloroquine and hydroxychloroquine pigmentation. Its characteristics are evident, since it can also be found in other regions of the body, and it is a hereditary manifestation differing from the pigmentation treated in this article, its intensity varies according to differences in gene expression.

The pigmentations can vary from intense and dispersed dark freckles to solitary pigmented patches [20] [21] [22] [23], developing in early childhood [15], unlike the studies involved in **Table 1** where the average age was 55.5 years. Its diagnosis is made by exclusion, considering non-smoking patients, non-users of drugs with potential for oral pigmentation, and age. The presence of pigmentations in other areas of the body, as well as the evaluation of family history in relation to the disease must be verified, emphasizing the importance of physical examination of the entire mouth, lips, face, and limbs. Biopsy need not be considered unless there is doubt concerning the diagnosis.

4.3.2. Racial Melanic Pigmentation

Where there is excessive deposition of melanin in the melanocytes, leading to skin pigmentation, being common to black individuals, normal variation is considered. This is characterized by darkened and well-defined macules, mainly in the anterior buccal gingival region that usually present bilaterally, whether in small or large dimensions [15]. The location and predilection for black individuals are observed as differences between chloroquine and hydroxychloroquine pigmentation. Melanic pigmentation presents a certain degree of difference from other pigments, both because of its involvement, which is usually restricted to black individuals, and its history of evolution, which resembles that of a benign lesion. Once the diagnosis of racial pigmentation is complete, no treatment is necessary, except in patients seeking gingival aesthetics.

4.3.3. Addison's Disease

Another disease with manifestations of multiple, small and blackish pigments is Addison's disease; presenting as flat melanic pigments, diffuse, and mainly in the cheek mucosa. Differential diagnosis includes racial melanin pigmentation, tobacco-related pigmentation, drug-related pigmentation, type 1 neurofibromatosis, McCune-Albright syndrome and Peutz-Jeghers syndrome [21]. Addison's disease is differentiated from chloroquine and hydroxychloroquine pigmentation by its presentation of multiple small pigmentations. An exam for evaluation is the morning serum cortisol level, which if it results in values above 500 nmol/L (18 μg/dL), generally excludes Addison's disease, if below 165 nmol/L (6 μg/dL) it is suggestive of renal insufficiency. However, most patients will need a brief Sinac test to confirm or exclude Addison's disease. In this case, the incisional biopsy is of great help in the diagnosis, and in the case of a positive diagnosis for Addison's disease, the patient should be referred quickly for medical follow-up. Pigmented lesions are usually neglected, despite their severity. Pig-

mented lesions can be isolated, multifocal, and of different sizes. Approaches for blackish, brown or brownish lesions differ according to the lesion's characteristics, since lesions with this aspect might turn out to be a malignant, such as melanoma. In a single small lesion (<5 mm) close to an amalgam restoration, it is good to request a radiographic examination to analyze the presence of radiopaque granules and, if they are present, the diagnosis of amalgam pigmentation is confirmed [22] (Meleti *et al.* 2008). If there is no radiopaque area, or if the lesion region is in the hard palate and/or the maxillary gingiva, incisional biopsy must be considered, since these are the most common sites for oral nevi and melanomas. In small multiple lesions with a likelihood of racial pigmentation, smoking, systemic conditions, or medication use, biopsy is not necessary (**Figure 5**) [22] [23] (Meleti *et al.* 2008; Hatch *et al.* 2005). In the case of large lesions, larger than 5 mm and located in the region of the palate and/or maxillary gingiva, it is essential to use the ABCD technique to detect a possible melanoma (**Figure 6**) [24] (Elwood *et al.* 1996).

The technique consists of assessing the lesion and seeing if it has an "A" asymmetry in its presentation due to the uncontrolled growth of melanoma. A letter "B", has irregular edges, "C", presents coloration in hues, ranging from brown to black, and "D", presents a diameter greater than 5 - 6 mm [24] [25] [26] (Elwood *et al.* 1996; Thomas *et al.* 1998). If there is correlation in the evaluation, incisional biopsy is essential.

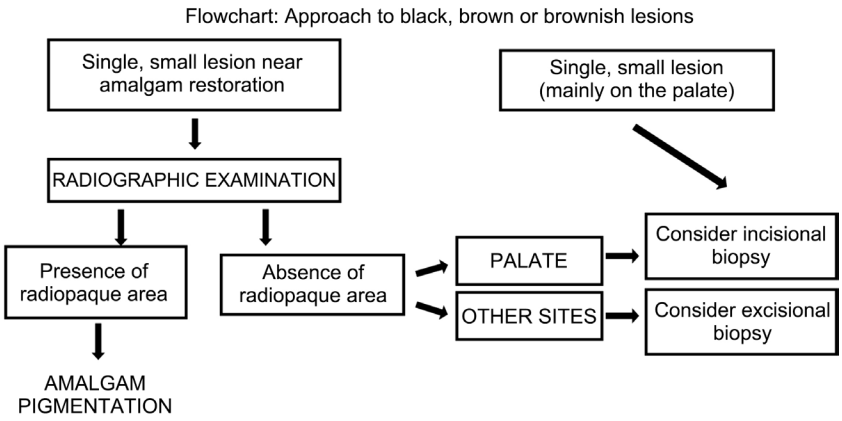

Figure 5. Algorithm for assessing pigmentation in the oral cavity.

Figure 6. Melanoma in a rare site (MISIR *et al.* 2016).

5. Conclusion

To arrive at a diagnosis for pigmented lesion in the oral cavity, meticulous anamnesis prior to physical examination is extremely important. In this pandemic and post-pandemic period, a more detailed investigation of the medications used by the patient in recent periods, such as chloroquine and hydroxychloroquine is essential to detect if the injury was possibly caused by these drugs. In case of doubt regarding the diagnosis, a biopsy is indicated.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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