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ORIGINAL ARTICLE

Pathological pigmentation of the skin and palate caused by continuous use of chloroquine: Case Report

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Abstract:

Introduction: Chloroquine diphosphate is an antimalarial drug commonly used in the treatment of autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis. Chronic use of this drug may cause toxicity and lead to irreversible visual loss. **Objective:** To report a case of pathological pigmentation of the skin and oral mucosa caused by the use of chloroquine diphosphate. **Case report:** A 40-year-old female patient used daily doses of chloroquine (250 mg) to treat rheumatoid arthritis. After using this antimalarial drug for two years, the patient exhibited pathological pigmentations in the hard palate and skin of the lower limbs. To prevent retinal damage, given the toxicity observed in the skin and mucous membranes, the medical team replaced this antimalarial drug. **Conclusion:** Pathological pigmentation is a sign of drug toxicity and may serve as a warning for health professionals in order to prevent macular diseases caused by antimalarial agents. We emphasize the importance of dental surgeons for the differential diagnosis of pathological pigmentation of the oral mucosa, as well as the importance of multidisciplinary work involving other health sectors to prevent the onset or worsening of clinical problems in these patients.

Keywords: Pigmentation; Chloroquine; Antimalarials; Drug Toxicity.

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INTRODUCTION

Oral mucosal pigmentation can arise due to different pathologies, such as Peutz-Jeghers syndrome, Kaposi's sarcoma, nevus, and melanoma. In addition, it can be induced by systemic drugs, such as some antineoplastic, antimicrobial, and antimalarial drugs[1].

Chloroquine diphosphate is an antimalarial drug used in the treatment of several autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis[2]. In Brazil, this drug is part of the first-line treatment of rheumatoid arthritis and is widely used by the Unified Health System of that country due to its effectiveness and low cost, especially when associated with other drugs[3].

Individuals who require continuous use of this drug may exhibit pathological pigmentation of the face, upper and lower limbs, and also some mucous membranes, such as the oral mucosa. These are changes that evolve from isolated macules to major lesions that can appear on the lips and, mainly, in the palate[4-8]. In addition, patients may develop irreversible retinal damage[9,10].

The purpose of this study was to report a case of a patient who developed palatal pigmentation after chronic use of antimalarial drug chloroquine and discuss potential side effects, raising awareness of therapeutic and preventive measures.

CASE REPORT

The present study was approved by the Research Ethics Committee of the Franciscan University Center, under Opinion No. 497,766. A 40-year-old, female, brown-skinned patient sought dental care in a higher education institution of Santa Maria, State of Rio Grande do Sul, Brazil.

The patient's main complaint was dissatisfaction with the appearance of her lower teeth. During anamnesis, the patient reported being a smoker with a consumption of about five cigarettes a day for five years. The medical record confirmed that the patient had rheumatoid arthritis and had been treated with 250 mg of chloroquine diphosphate and 10 mg of prednisone (continuous daily use) for two years, associated with subcutaneous injections of methotrexate solution every eight days.

The intraoral examination revealed a grayish-blue pigmentation of the hard palate (Figure 1). In addition, the patient also exhibited grayish-blue pigmentation in the lower limbs (Figure 2). An incision biopsy was performed in the palatal mucosa with a 4-mm punch and sent for histopathological analysis.

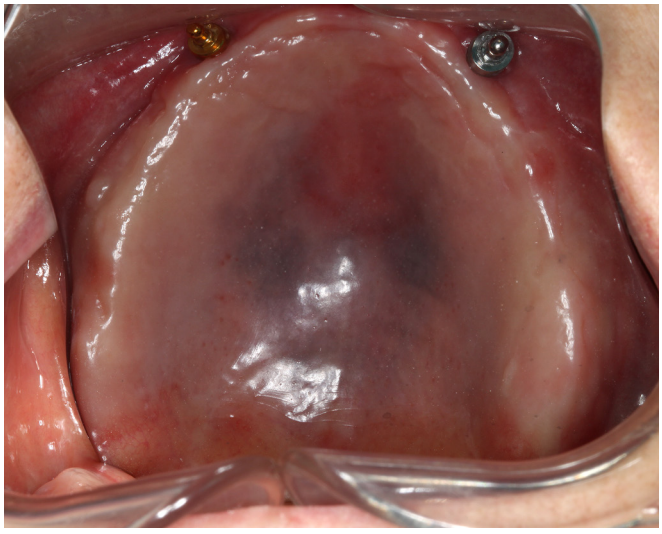

Figure 1. Blue-gray pigmentation on hard palate.

The exam showed brownish pigment deposition in the epithelial basal, as well as in the connective tissue, mainly in the perivascular region (Figure 3). These histological findings, associated with the clinical history, confirmed the diagnosis of drug-induced pigmentation (chloroquine). After the histopathological diagnosis, an ophthalmologic evaluation was requested. It was found that the patient already had myopic degeneration in the left eye; however, there were no ocular changes related to the use of chloroquine.

The rheumatologist was informed about the intraoral and skin pigmentations and the ophthalmologic examination, and decided to change the therapeutic scheme for rheumatoid arthritis in order to prevent eye injuries. The treatment with chloroquine diphosphate was replaced with 20 mg/day of leflunomide. Methotrexate and prednisone were kept with the same dosage. Currently, the patient visits the dental surgeon once a year and is followed up by the rheumatologist and the ophthalmologist.

DISCUSSION

Oral pigmentation caused by antimalarial drugs was reported for the first time in 1945 by soldiers who were in the South Pacific and had been treated with quinacrine hydrochloride[11]. Several subsequent clinical case reports were published reporting oral pigmentation induced by continuous use of antimalarial drugs, such as hydroxychloroquine sulfate and chloroquine diphosphate[4-8].

In the present case, the pathological pigmentation in the palatal mucosa had been induced by chloroquine

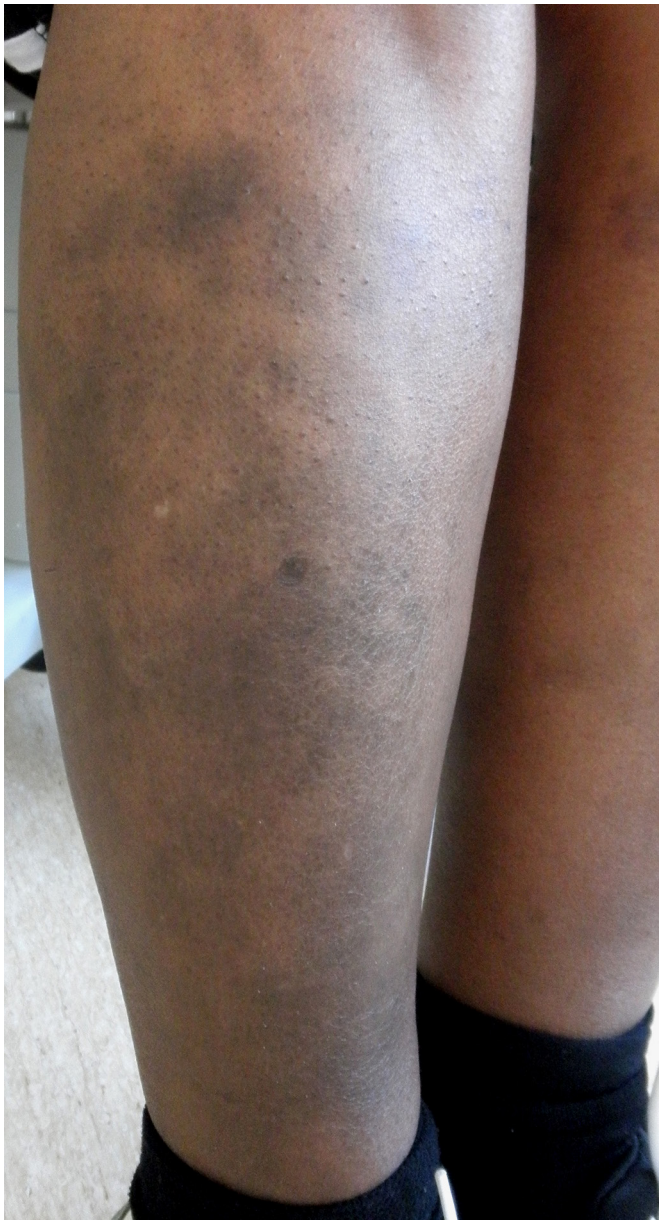

Figure 2. Blue-gray pigmentation in lower right limb.

diphosphate. This drug has been widely used in the treatment of rheumatoid arthritis, classified as "synthetic disease-modifying antirheumatic drugs", and is part of first-line treatment of rheumatoid arthritis in initial stage[3].

The pigmentation of the oral mucosa caused by antimalarial drugs is usually asymptomatic, colored blue and gray, and exhibit a remarkable demarcation between the soft and hard palate. Even though the palatal mucosa is the site with greatest occurrence, the literature does not provide a plausible explanation for the appearance of pigmentation mainly in this region[4-8].

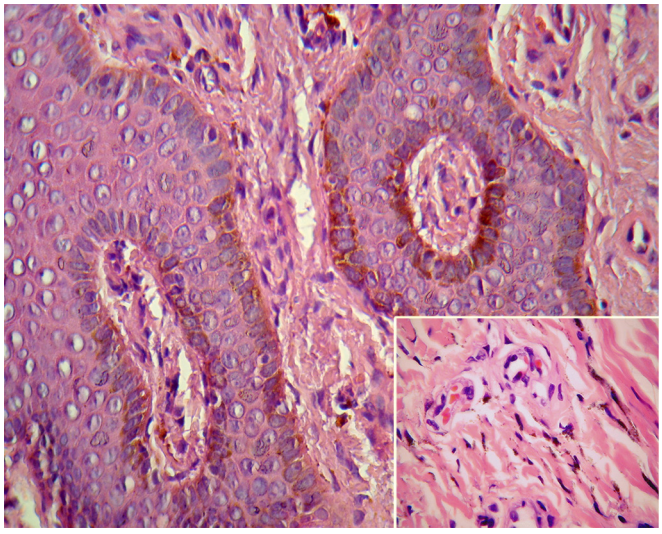

Figure 3. Deposition of brownish pigment in the basal layer of the epithelium and in the connective tissue, especially in the perivascular region (insert). Hematoxylin and eosin, 400x.

Often, this drug-induced pigmentation is more blackened and exhibits irregular edges, whose aspect is similar to that of melanomas[12]. This fact reinforces the importance of accurate diagnosis, as well as the performance of biopsy and histopathological analysis to make the differential diagnosis with other pathologies.

In the present case, the drug also caused pigmentation of the lower limbs of the patient. This occurrence has been described with some frequency by other authors, who, although less frequently, have also reported the occurrence of pigmentation in hands, face, and upper limbs[12-14]. The clinical aspects of the lesions in these areas range from dark purple to grayish blue, with the progression from isolated macules to major lesions. The pathogenesis of pigmentation caused by these drugs is still unknown; however, studies have demonstrated that there is a high accumulation of iron in affected tissues in comparison to normal tissues, as well as increased melanin and hemosiderin deposition dispersed in the extracellular matrix or within macrophages[5,14].

Although antimalarial drugs are really efficient in the treatment of certain autoimmune diseases, chronic use of these drugs can also cause irreversible retinal damage[9,10]. This fact occurs because chloroquine and hydroxychloroquine have affinity with melanin contained in the ciliary body, the coronoid and the retinal pigment epithelium, where they settle and may remain deposited for a long time, even after completion of treatment[15].

Retinal toxicity is less associated with the use of hydroxychloroquine sulfate when compared to prolonged use of chloroquine diphosphate, and is also related to

the time during which the drugs has been used and the daily doses[9,10,14,15]. Although many studies suggest that ocular toxicity caused by chloroquine is greater than that caused by hydroxychloroquine, there is no evidence that allows determining the safe dosage for the use of hydroxychloroquine and chloroquine.

However, a recent update performed by the American Academy of Ophthalmology on the recommendations for the screening of retinopathy in patients with chronic use of chloroquine and hydroxychloroquine[9] recommends a maximum of 5 mg/kg (real weight) of hydroxychloroquine, and a maximum of 2.3 mg/kg (real weight) of chloroquine as the safe daily doses. Taking into consideration that chloroquine diphosphate is supplied as 250-mg tablets, the dosage taken by almost all the patients is higher than the safe dosage recommended[9].

Patients at advanced ages should be monitored more carefully, because they may be subject to macular degeneration caused by aging, thus increasing the chances of pharmacological retinopathy. In addition, a differential diagnosis between a senile degenerative disease and a disease resulting from the use of the drug can be difficult[10,15].

Currently, the American Academy of Ophthalmology recommends that all patients who start treatment with antimalarial drugs should undergo a prior ophthalmologic assessment to discard a preexisting maculopathy. According to evidences[9], there is no need for ophthalmologic monitoring within the first five years when there is not a major risk factor, such as excessive dosage of the drug. After that time, the patients should undergo annual ophthalmologic examinations.

In the case reported in the present study, there was a major risk factor (dosage above the safety limit) and pathological pigmentation of skin and mucous membranes, even after having used the drug for a short time. This fact called the attention of the dental professionals and they chose to replace the antimalarial drug with another drug classified as "synthetic disease-modifying antirheumatic drugs".

In this context, the dental assessment of patients who use these drugs should be meticulous to allow the identification of a possible pathological pigmentation of the oral mucosa and skin, and promote early ophthalmologic assessment. In addition, since maculopathy caused by antimalarial drugs is irreversible and has no treatment until present[9], we emphasize the importance of early detection of retinopathy, whose cellular damage can progress even after drug withdrawal. The identification of retinopathy in early stages is essential to minimize the progression of retinal damage after drug withdrawal and reduce the loss of visual acuity.

Although skin and oral mucosal pigmentation caused by chronic use of chloroquine are apparently innocuous with only aesthetic implications, the identification of these pigmentations by clinicians is essential and may serve as a warning in order to encourage the medical team to investigate in advance the possible occurrence of other serious side effects and thus prevent irreversible damage.

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