

Bichat. Advantages of using buccal fat pad include easy access, low morbidity, high success and no need for any additional donor site<sup>12</sup>.

The prognosis for verrucous carcinoma is excellent, primarily because of its high level of differentiation and rarity of metastatic spread. Local recurrence, however, remains a distinct possibility if inadequate treatment is rendered.

## CONCLUSION

Oral verrucous carcinoma requires a close team approach of the surgeon and the pathologist for better, effective and efficient care for the patient. Adequate wide local excision and close follow up are essential part of care and go a long way in preventing any recurrence of the lesion.

## REFERENCES

- 1) Alper Alkan, Emel Bulut et al; Oral Verrucous Carcinoma: A Study of 12 Cases; Eur J Dent. 2010 Apr; 4(2): 202-207.
- 2) Chung-Jan Kang, MD, Joseph Tung-Chieh Chang; Chang Gung; Surgical Treatment of Oral Verrucous Carcinoma; Med J 2003; 26:807-12
- 3) Azevedo LH, Gallettave et al; Treatment of Oral verrucous carcinoma with carbon dioxide laser; J Oral Maxillofac Surg. 2007 NOV; 65(11); 2361-6
- 4) Walvekar RR; Verrucous carcinoma of the oral cavity: A clinical and pathological study of 101 cases.; Oral Oncology 2009; 45:47- 51
- 5) N Kaushal, N Madan; Verrucous carcinoma of the oral cavity; The Internet Journal of Geriatrics and Gerontology. 2009 Volume 6 Number 1
- 6) Depprich RA; Hanschel JG et al; Hybrid Verrucous Carcinoma of the oral Cavity : A challenge for the clinician and the pathologists; Oral Oncology Extra; 2006; 42; 85-90
- 7) Ackerman LV; Verrucous carcinoma of the oral cavity; Surgery 1948; 23(4); 670-8
- 8) Hsin-Ming Chen, Chuan-Hang Yu et al; 5 -Aminolevulinic acid - mediated photodynamic therapy for oral cancers and precancers. Review article; Journal of Dental Sciences, Volume 7, issue 5, December 2012; 307-15
- 9) Heinzerling LM; Kempf W et al; Treatment of Verrucous Carcinoma with Imiquimod and CO2 laser ablation; Dermatology; 2003; 207(1) 119-22
- 10) Chuan-Hang Yu, Hung-Pin Lin; Cryotherapy for Oral precancers and cancers; Review article; Journal of the Formosan Medical Association, Volume 113, issue 5, may 2014, 272-277
- 11) Mehra P; Buccal fat pad graft our experience in reconstruction; IJOMS; Nov 2007; 36; 11; 1058
- 12) Kevin A; Buccal fat Pad In Maxillary Reconstruction; Atlas of oral and maxfac. surgery clinics of North America; march 2007; 15; 1

## Extensive Multifocal Minocycline - associated Oral and Cutaneous Pigmentations.

Hardeep Chehal, Mohammed N. Islam, Sarah Islam, Indraneel Bhattacharyya

Department of Oral and Maxillofacial Diagnostic Sciences, University of Florida College of Dentistry  
PO Box 100414, 1395 Center Drive, Gainesville, FL 32610

### INTRODUCTION

Minocycline, a tetracycline family antibiotic, is most commonly used for the long term treatment of several skin ailments including acne vulgaris and rosacea.<sup>1</sup> Although minocycline is highly effective, a major esthetically concerning and well-documented side effect is diffuse pigmentation of multiple tissue and fluids including skin, subcutaneous fat, nails, teeth, gingivae, oral mucosa, lips, conjunctiva, sclera, and bone.<sup>2</sup> The underlying pathophysiology remains unclear.<sup>2,3</sup> Skin pigmentation may be exacerbated by sunlight, suggesting that preventive use of sunscreens may be useful for patients undergoing minocycline therapy.<sup>3</sup> Minocycline related skin pigmentation is a potentially disfiguring side effect of an otherwise highly effective medication and the oral pigmentation associated with it can be of major concern and anxiety to the patient.<sup>4</sup> It is advisable to closely monitor the patient on long term minocycline use for development of pigmentation.<sup>3</sup> We present a case of significant mucocutaneous pigmentation in a Caucasian female involving the skin of the foot and lower legs, with extensive involvement of the oral mucosa as well. We also discuss minocycline-induced oral pigmentation and other causes of similar pigmentations.

### CASE REPORT

A 52 year old Caucasian female was seen in the oral diagnosis clinic for a routine oral exam. The patient's medical history included fibromyalgia, breast cancer, and seizures, as well as depression and bipolar disorder. Breast cancer was diagnosed approximately one year ago and had been subsequently treated with radiation and a lumpectomy. Treatment for her other conditions has been ongoing. Her medications included lorazepam, diazepam, cyclobenzaprine, risperdal, minocycline, famotidine, lamictal, topiramate, valacyclovir, and simvastatin. The patient did not remember any major illnesses or taking any medications as a child. She did not report any systemic symptoms and appeared to be in good health at the time of examination.

Clinical examination revealed a large macule with irregular borders and a bluish black discoloration on the dorsal skin of the left foot (Figure 1). She also presented with similar macules on her lower extremities which were multifocal, smaller in size, and lighter in color compared to the one on her foot (Figure 2). The onset of these cutaneous macules was approximately more than 2 years ago. Her face and upper extremities were devoid of any similar lesions. Intraoral examination revealed multifocal, poorly defined, bluish-black macular pigmentations bilaterally on her buccal mucosa (Figure 3). Her maxillary and mandibular gingivae were also discolored and the discoloration extended anteriorly to her mandibular incisor teeth (Figures 3 and 4).

An incisional biopsy obtained from the left buccal mucosa

**Correspondence:** Dr. Indraneel Bhattacharyya, Associate Professor  
Department of Oral and Maxillofacial Diagnostic Sciences, University  
of Florida College of Dentistry, PO Box 100414, 1395 Center Drive,  
Gainesville, FL 32610  
e-mail: ibhattacharyya@dental.ufl.edu



**Figure 1:** Extraoral examination revealed a large macule with irregular borders and a bluish black coloration on left foot.



**Figure 2:** Multifocal, irregular, bluish-black macules on the lower extremity.



**Figure 3:** Intraoral examination revealed irregular bluish black macules on her buccal mucosa.



**Figure 5:** Intraoral examination revealed diffuse discoloration of her mandibular attached gingiva as well as her anterior teeth.

monstrated aggregates of melanin in the basal cell layer as well as in the superficial lamina propria. A concomitant increase in number of melanocytes was not noted. Based on the clinical and microscopic findings, a diagnosis of drug induced melanosis was rendered as this type of diffuse multifocal pigmentation has been reported with minocycline, which the patient had been using.

## DISCUSSION

Many medications are reported to induce skin and/or mucous membrane discoloration<sup>1</sup>. The chief drugs implicated in causing skin pigmentation are nonsteroidal anti-inflammatory drugs, antimalarials, amiodarone, cytotoxic drugs, tetracyclines, heavy metals, and psychotropic drugs<sup>1</sup>.

Minocycline is a semisynthetic tetracycline. It was first introduced in 1967 and, like other tetracyclines, minocycline has an antimicrobial, anti-inflammatory, and immunosuppressive effect, and is primarily used to treat acne vulgaris.<sup>2</sup> This medication has several advantages over others within the same class in that it is better absorbed, has increased antimicrobial activity, and little to no phototoxicity.<sup>3</sup> It is lipid soluble, allowing for easy penetration into body fluids such as saliva and gingival crevicular fluid, as well as into various body tissues including bone and soft tissues.<sup>3,4</sup> Apart from acne, minocycline has also been used to treat other inflammatory and immune disorders. The most well recognized adverse effect of tetracyclines, particularly minocycline, is its potential to cause pigmentation of the skin, bone, teeth and sclera.<sup>3,4</sup> The extent of pigmentation is not related to dose and duration.<sup>3</sup> Mucocutaneous pigmentation secondary to minocycline therapy has been reported previously. Cutaneous pigmentation resulting from minocycline therapy consist of 3 basic forms: Type I, blue-black macules in relation to sites of inflammation, Type II, blue-black macules on extremities, and Type III, diffuse brown-grey macules on sun exposed skin.<sup>3</sup>

However, most intra-oral cases described in the literature deal primarily with pigmentation of the hard tissues such as alveolar bone, roots, and crowns of teeth. The most commonly affected oral anatomic site as per literature is the alveolar bone, which presents with a characteristic black discoloration. Oral pigmentation additionally involves the soft tissues as

well as hard tissues. Soft tissue pigmentations are most frequently seen on the maxillary and mandibular gingiva and the dorsal and lateral surfaces of the tongue. Our case showed pigmentation on these sites, as well as on the buccal mucosa. Affected oral hard tissues include the alveolar bone as well as the teeth. Unlike tetracyclines, fully formed and erupted teeth may also be discolored by minocycline.<sup>4</sup> This appears to have been the case in our patient.

Several mechanisms have been proposed in the drug-induced pigmentation of the skin and mucosa.<sup>5</sup> The exact mechanism of minocycline-induced pigmentation remains unknown. Ultrastructural and x-ray microanalyses by some investigators have implicated hemosiderosis, which may be a result of microhemorrhage secondary to cutaneous trauma. Other researchers have identified insoluble complexes of minocycline or a derivative chelated with iron within the dermis. Another mechanism suggests that minocycline, due to its unique chemistry, may form reactive metabolites—in particular, a quinone iminium ion, along with other reactive species, may polymerize to form a black pigment and contribute to the formation of autoantibodies involved in idiosyncratic reactions of minocycline.<sup>5</sup>

It is vital for the clinician to recognize this medication-related condition to avoid confusion with other systemic conditions causing similar pigmentations. It is also important to remember that the oral soft tissue and cutaneous pigmentations associated with minocycline-related complications are reversible. Unfortunately, such reversal has not been reported in the hard tissues, so timely reorganization and medication substitution are helpful in preventing future esthetic concerns and unnecessary restorative treatment.<sup>3</sup>

When extensive intraoral pigmentation is noted, it is important to consider physiological (racial) pigmentation in the differential diagnosis. This is the most common form of intraoral pigmentation and is generally seen on the oral mucosa of dark-skinned individuals, with gingiva being the preferred site. Hyperpigmentation of the buccal mucosa may be seen in approximately 5% of the Caucasian population as well.<sup>1</sup> The pigmentation pattern is typically symmetric, diffuse or multifocal, and uniform. Different ethnic groups show variable prevalence, and the intensity of pigmentation increases with age. The resulting pigmentation is a result of increased melanocyte activity rather than an increase in the number of melanocytes. It is important to consider that this lesion in the clinical differential diagnosis of oral pigmentations since it is primarily a clinical diagnosis and a biopsy is indicated only if the clinical features are atypical.<sup>1,2</sup>

In addition, oral melanoacanthomas can also present intraorally as areas of hyperpigmentation.<sup>6</sup> Melanoacanthoma are rare, benign, usually solitary lesions which are usually seen in dark-skinned adult population with a female predilection. In recent reports, the lesion has also been seen in ethnic and racial groups other than African Americans.<sup>6</sup> The lesion presents as dark-brown pigmented plaque on buccal, palatal, and gingival mucosa. Though the etiology is not clear, typically traumatic irritants have been implicated as the causative factors, and the lesion generally regresses after removal of the irritants or after excisional biopsy. Acanthosis, basal cell layer hyperpigmentation and presence of large-pigment laden melanocytes are seen microscopically throughout the lesion which correlates with the brown clinical appearance of the lesion. It is important to recognize this lesion because its rapid increase in size (develops within a few weeks) is a concern to both the patient and clinician. A biopsy is usually needed for a precise diagnosis and to eliminate the possibility of a melanoma.<sup>6</sup>

A wide variety of metabolic and endocrine diseases may also result in diffuse pigmentation (dyschromia) of mucous membranes and skin

including Addison disease, hemochromatosis, Wilson disease, jaundice, Peutz-Jegher syndrome, etc.<sup>1,7,8</sup> Usually these can be confirmed by laboratory investigations. Important among these is Addison disease which is a rare condition resulting from adrenal insufficiency. The destruction of the adrenal gland may be of primary or secondary etiology and results in cortisol deficiency. Increased adrenocorticotrophic hormone (ACTH) and beta-lipotropin levels result from adrenal gland damage and stimulate melanocytic activity. Cutaneous affects range from hyperpigmentation to hypopigmentation. Generalized hyperpigmentation, also known as "bronzing of the skin," is seen in almost 90% of the cases and is of insidious onset, diffuse and predominantly seen on sun-exposed areas.<sup>1</sup> Oral pigmentation may be the first sign of the disease and is often a prominent feature.<sup>1</sup> The presentation may range from macules or streaks of blue-black pigmentation on any oral mucosal site. Nails and genital mucosa may also be affected. Treatment with corticosteroid replacement therapy results in a gradual reduction of cutaneous pigmentation. Oral pigmentation may, however, persist. The importance in recognizing this condition lies in its timely management.<sup>1,8</sup>

Consideration should also be given to Peutz-Jeghers syndrome (PJS) which represents an autosomal dominant hereditary disorder. However, 50% of patients have no family history of the syndrome.<sup>7</sup> This syndrome consists of intestinal polyposis and characteristic mucocutaneous pigmentation. Mucocutaneous melanocytic lesions are seen in 95% of the patients. They may not be present at birth and typically become prominent by 5<sup>th</sup> year of life eventually may fade away by puberty.<sup>7</sup> When present, the pigmentations are seen around the mouth and nostrils, perianal area, the fingers and toes, as well as the buccal mucosa.<sup>7</sup>

## CONCLUSIONS

Minocycline pigmentation should be recognized and all patients receiving the drug should be closely monitored if the patient has been on therapy for longer than one year. The drug should be discontinued promptly if pigmentation is recognized. Skin pigmentation usually resolves within a year whereas pigmentations in other body parts tend to be permanent. If properly monitored, minocycline is a useful drug for treatment of acne and rosacea.

## REFERENCES

1. Neville BW, Damm DD, Allen CM, Bouquot JE. *Physical and Chemical Injuries*. In: Neville BW, Damm DD, Allen CM, Bouquot JE, editors. *Oral and Maxillofacial Pathology*. 3rd ed. St. Louis, MO: Saunders; 2009. p. 317-18.
2. Treister NS, Magalnick D, Woo SB. Oral mucosal pigmentation secondary to minocycline therapy: report of two cases and a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2004;97(6):718-25.
3. Eisen, D, Hakim MD. Minocycline-induced pigmentation. *Drug Saf*. 1998;18(6):431-40.
4. Hung PH, Caldwell JB, James WD. Minocycline-induced hyperpigmentation. *J Fam Pract* 1995;41(2):183-5.
5. Shapiro LE, Utrecht J, Shear NH. Minocycline, perinuclear antineutrophilic cytoplasmic antibody, and pigment: the biochemical basis. *J Am Acad Dermatol* 2001;45:787-9.
6. Carlos-Bregni RI, Contreras E, Netto AC, Mosqueda-Taylor A, Vargas PA, Jorge J, León JE, de Almeida OP. 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):E374-9.
7. Jenne DE, Reimann H, Nezu J, Friedel W, Loff S, Jeschke R, et al. Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. *Nature genetics* 1998;18(1):38-43.
8. LaPorta VN, Nikitakis NG, Sindler AJ, Reynolds MA. Minocycline-associated intra-oral soft-tissue pigmentation: clinicopathologic correlations and review. *J Clin Periodontol*. 2005;32(2):119-22.



### Our Key Products

**Oriva**  
Nephrocare

**RENOPHILUS**<sup>TM</sup>  
Probiotic 90 Billion CFU

**KETODEL**<sup>TM</sup>  
Alpha Ketoanalogue Tablet

**Q-TINE**<sup>TM</sup>  
Coenzyme Q<sub>10</sub> + L-Carnitine

**GLUTAFIT**<sup>TM</sup>  
L-glutamine 10g + Vit. A 5000 IU + Vit. E 120 IU

**AVRON**<sup>TM</sup>  
Injection Iron Sucrose 20mg/ml

**ORITROL**<sup>TM</sup>  
Calcitriol 0.25 mcg

**RENFOL**<sup>TM</sup>  
Folic Acid 10mg Ferrous ascorbate  
100mg + methylcobalamin 500mg  
+ B complex

**ORISIS**<sup>TM</sup>  
Sodium bi carbonate 500mg

**ORIPRO**<sup>TM</sup>  
High Protein Formula 61gm/serving

For Further Information:  
[www.orivalifesciences.com](http://www.orivalifesciences.com)  
Helpline No. : 99530 45902

**ORIVA LIFESCIENCES PVT. LTD.**  
206 National Arcade, Plot No. 4,  
LSC Ghazipur, Delhi-110096

*Presenting*

The proven therapy to delay progression of

## **Chronic Kidney Disease**

# **Ketosteril<sup>®</sup>**

**Protects and Preserves Renal Function**

- **Provides nitrogen sparing effect**
- **Reduces hyperfiltration of nephrons**
- **Improves metabolic complications**



*Recommended for all patients with:*

- **Proteinuria, even micralbuminuria**
- **Creatinine clearance < 50 ml/min**

**Delays the onset of dialysis and Prolongs life expectancy**

Dose: 1 tab/5kg bw/day



**Fresenius  
Kabi**  
Caring for Life

For further detailed information please contact

**Fresenius Kabi India Pvt. Ltd.**

Heritage House, 6-E, Ramabai Ambedkar Road, Pune - 411001, India

Ph. : 91-20-26053602-7 Fax : 91-20-26138258

[www.fresenius-kabi-india.com](http://www.fresenius-kabi-india.com)