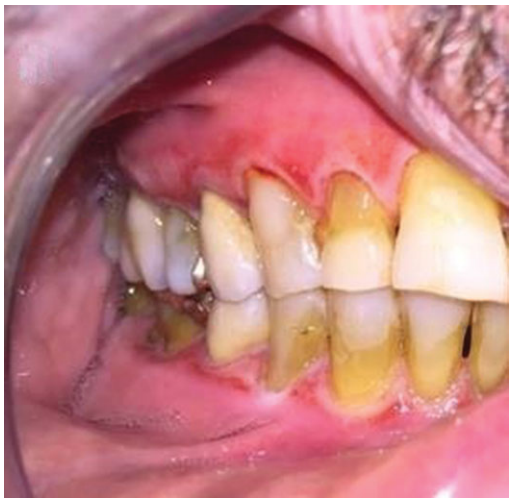
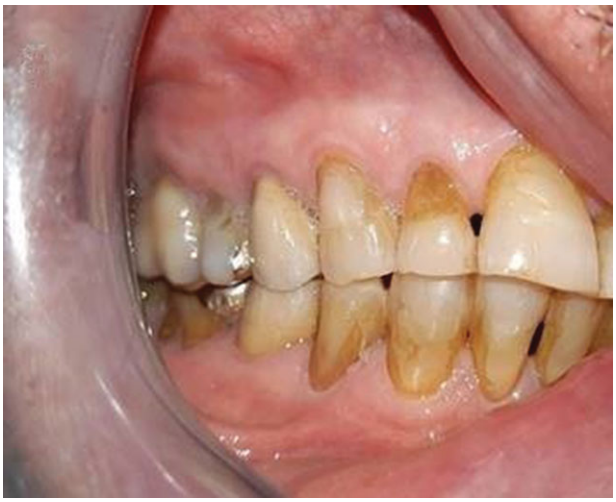
Gingival Ischemia and Petechiae in a Patient Medicated with PCSK9 Inhibitor for Hypercholesterolemia. An Adverse Drug Event?

Grigoris Thermos* and Konstantinos I. Tosios*





Introduction: Monoclonal antibodies against proprotein-convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a newly-introduced therapeutic approach against hypercholesterolemia. Clinical trials have reported few adverse effects of PCSK9 inhibitors and there are no reports of oral adverse effects. We present the case of a patient that showed gingival discomfort on eating and toothbrushing, coupled with the presence of gingival ischemia and petechiae, 3 days after a subcutaneous abdominal injection of 75-mg alirocumab for hypercholesterolemia, and contemplate on their possible pathogenesis.

Case Report: An 81-year old male presented with gingival discomfort during eating and toothbrushing, 3 days after receiving a subcutaneous abdominal injection of alirocumab. Intraoral examination revealed that the anterior free and attached gingiva of both jaws appeared pale and the surrounding mucosa showed confluent petechiae that were more evident on the anterior palatal gingiva. The patient was asked to brush his teeth with a soft toothbrush and use a mouthwash containing hydrogen peroxide three times daily. At the 8-day re-examination he was symptom-free, and the mucosa appeared totally normal. At the 5-month follow-up visit he reported having the same symptoms after each one of the 12 doses of alirocumab he received.

Conclusions: Adverse dugs effects associated with subcutaneous injection of alirocumab may manifest in the gingiva. Therefore, oral and periodontal examination should be included in the regular follow-up of patients medicated with this drug. *Clin Adv Periodontics* 2018;0:1–4.

Key Words: Hypercholesterolemia; alirocumab; drug-related side effects and adverse reactions; mouth diseases; drug effects; gingival diseases.

Background

Monoclonal antibodies against proprotein-convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a newly-introduced therapeutic approach against hypercholesterolemia.[1] PCSK9 reduces low-density lipoprotein (LDL) receptors by promoting their metabolism and degradation in the hepatocytes, thus inducing high plasma concentrations of low-density lipoprotein C (LDL-C).[1] It has been related to atherogenesis, by either altering endothelial repair or neovascularization mechanism, or by reducing LDL-R expression in macrophages.[2–4] Furthermore, there is a correlation between free PCSK9 levels, inflammation[5] and white blood count[6] that are critical parameters in early atherogenesis and subsequent cardiovascular events.

The main indications for PCSK9 inhibitors prescription are homozygous and heterozygous familial

*Department of Oral Medicine and Pathology, Dental School, National and Kapodistrian University of Athens, Athens, Greece

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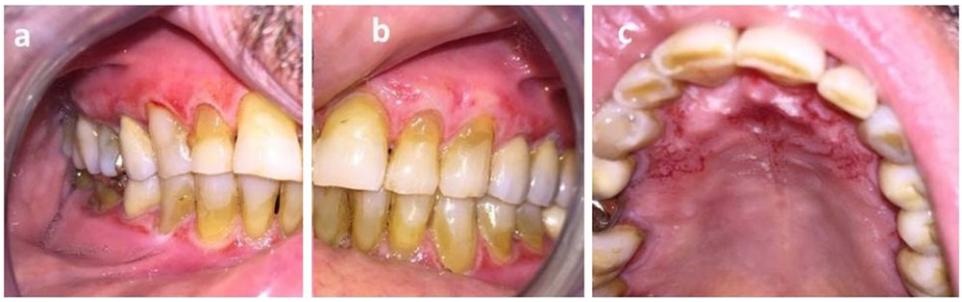

FIGURE 1 Intraoral picture. The anterior free and attached gingiva of both jaws appear pale and the surrounding mucosa shows confluent petechiae (**1a and 1b**) that are more evident on the anterior palatal gingiva (**1c**).

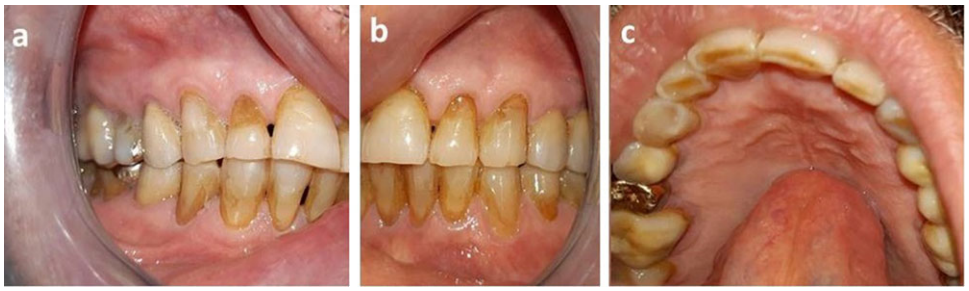

FIGURE 2 At the 8 days re-examination, the anterior gingiva (**2a and 2b**) and the palatal mucosa (**2c**) appear normal.

hypercholesterolemia, as adjuncts to statin-therapy and diet, and clinical atherosclerotic cardiovascular disease, where a greater reduction in LDL-C levels is required.[1] In 2015, the FDA approved the use of PSCK9 inhibitors alirocumab[†] and evolocumab[‡] for intravenous or subcutaneous administration, in a dose of 75 mg or 150 mg every 2 weeks, or 300 mg monthly, and 140 mg every 2 weeks, or 420 mg monthly, respectively.

PSCK9 inhibitors are newly introduced drugs and, to our knowledge, there are no accurate reports on their global prescription. In the United States, it is estimated that fewer than 220,000 patients were prescribed PCSK9 inhibitors in 2016.[7]

Adverse effects of PCSK9 inhibitors include hypersensitivity reactions, bacterial infections, such as nasopharyngitis and urinary tract infections, elevated liver enzymes and/or creatine kinase levels, musculoskeletal pain and contusion, as well as a higher incidence of neurocognitive disorders.[1] There are no reports of oral adverse effects of alirocumab.

We present the case of a patient that showed gingival discomfort on eating and toothbrushing, coupled with the presence of gingival ischemia and petechiae, 3 days after a subcutaneous abdominal injection of 75-mg alirocumab for hypercholesterolemia, and contemplate on their possible pathogenesis.

[†]Praluent, Sanofi-Aventis, Bridgewater, NJ

[‡]Repatha, Amgen, Thousand Oaks, CA.

Clinical Presentation

An 81-year old male was referred in October 2017 with a chief complaint of gingival discomfort during eating and toothbrushing. According to his account, the discomfort appeared 3 days after receiving a subcutaneous abdominal injection of alirocumab 75 mg. His medical history was remarkable for metabolic syndrome and high levels of uric acid. He was medicated for many years with amlodipine with olmesartan and nebivolol for hypertension; clopidogrel and aspirin for blood clotting; vitamin E, ezetimibe and co-enzyme 10 (Q10) for high cholesterol; and allopurinol for uric acid.

Intraoral examination revealed that the anterior free and attached gingiva of both jaws appeared pale and the surrounding mucosa showed confluent petechiae (**Figs. 1a and 1b**) that were more evident on the anterior palatal gingiva (**Fig. 1c**). The patient reported "discomfort" but not pain on friction, while no hemorrhage or sloughing of the mucosa were seen. There were no necrotic lesions or decapitated gingival papillae, no dental plaque or tartar, and no bad odor. Overall, his oral hygiene was very good. The rest of the oral mucosa was normal and there were no enlarged cervical lymph nodes. The patient did not report any other symptoms or signs, systemically or at the site of injection.

Case Management

Due to the mild symptoms and non-diagnostic clinical signs a regular follow-up was decided. A diagnostic biopsy was considered, but as the patient was medicated with anticoagulants and a vascular reaction was strongly suspected, it was not performed. The patient was asked to brush his teeth with a soft toothbrush and use a mouthwash containing hydrogen peroxide three times daily. The patient provided oral and written consent to participate.

Clinical Outcome

At the 3-day re-examination, he was symptom-free, the color of the gingiva was nearly normal, but hemorrhagic lesions persisted. At the 8-days re-examination, the mucosa appeared normal (**Fig. 2**) and the patient reported that he could eat and brush his teeth without any discomfort.

Laboratory tests performed 6 days after examination showed high levels of blood urea and creatine phosphokinase (CPK), and a slight increase in uric acid, creatinine, and triglycerides levels. The platelet count was normal, and the international normalized ratio (INR) was 2.7. His attending physician was informed about the possible association of the oral symptoms and signs with the drug, but as they were mild, a second dose was administered 2 days later.

At the 5-month follow-up visit, he reported having the same symptoms after each one of the 12 doses of alirocumab he received. As he experienced some serious adverse events, such as hypertension, myalgias, nausea, and diarrhea, he decided to refrain from further medication with alirocumab.

Discussion

In the case presented herein, gingival discomfort on eating and toothbrushing, associated with gingival ischemia and petechiae were seen in a patient 3 days after a subcutaneous abdominal injection of 75-mg alirocumab. This clinical presentation is not consistent with a specific oral disease and point to phenomena associated with the circulatory system. Temporal relationship with drug injection, resolution of the lesions after discontinuation of the drug, and recurrence each time it was administered are strongly suggestive of an adverse effect to alirocumab.

Contusion, i.e. extravasation of blood into the surrounding intestinal tissues due to traumatic disruption of small vessels, was recorded in large clinical trials in 2.1% of patients medicated with alirocumab, compared with 1.3% for placebo.[1] The site of contusion was not specified, while there are no theories on its possible pathogenesis. It may be hypothesized that alirocumab could negatively affect blood clotting after trauma, as PSCK9 positively affects platelets' activation and thrombosis.[8] In our case, hemorrhage developed in the masticatory mucosa of the gingiva and the palate, a commonly traumatized site of the oral mucosa, 3 days after the injection of the drug, when alirocumab reaches its maximum concentration and free PCSK9 its minimum level,[9] while the patient was synchronously medicated with two antiplatelet drugs, clopidogrel and aspirin. This hypothesis cannot explain the lack of hemorrhage in other commonly traumatized intraoral sites, such as the buccal mucosa and the tongue, or ischemia. The latter could be related to local vasoconstriction. In vitro, downregulation of PCSK9 inhibits endothelial nitric oxide synthase (eNOS) activation in endothelial cells exposed to lipopolysaccharides (LPS)[10] and in rats' gingiva it has been shown that eNOS causes vasodilatation through smooth muscle relaxation.[11] It may be, thus, theorized that inhibition of PSCK9 consecutively inhibited eNOS causing vasoconstriction and ischemia in the gingiva, where microbial inflammation and LPS are constantly present.[12] A combination of the antiplatelet and vasoconstrictive actions of alirocumab may explain the gingival signs in our patient.

Vasculitis is a common drug-related adverse effect, characterized by vessel inflammation and necrosis.[13] Monoclonal antibodies used as therapeutic agents are increasingly implicated in vasculitis[14] and vasculitis is a known side effect of alirocumab, although its incidence is not known.[1] Drug-associated vasculitis may range from a localized cutaneous vasculitis to a severe life-threatening syndrome with multiple organ involvement.[13,14] Cutaneous vasculitis has no diagnostic clinical, laboratory, or pathologic finding.[13] It usually manifests with hemorrhagic lesions, in particular palpable porphyra that may be accompanied by gastrointestinal (GI), joint, and kidney involvement. Withdrawal of the offending agent is usually curative. An immunocomplex deposition/type III hypersensitivity reaction is considered as the most probable pathogenetic mechanism.[13] Anti-alirocumab antibodies were observed in 155 of 3,039 patients (5.1%) medicated with the drug.[15] Therefore, it seems possible that in our patient anti-alirocumab antibodies were produced that formed immunocomplexes with the drug. The latter were preferentially deposited in the vessels of the inflamed gingiva, causing both ischemic lesions due to necrosis, as well as hemorrhage manifesting with petechiae. It should be noted that in our case alirocumab treatment was discontinued as the patient experienced adverse events from the GI tract and the joints, findings consistent with vasculitis.[13]

Conclusions

Adverse dugs effects associated with subcutaneous injection of alirocumab may manifest in the gingiva. Therefore, oral and periodontal examination should be included in the regular follow-up of patients medicated with this drug.■

Summary

Why is this case new information?	■ This is the first report of a possible oral side effect of PCSK9 Inhibitors, a novel class of drugs used in the treatment of hypercholesterolemia.
What are the keys to successful management of these cases?	■ Identification of the possible association of the oral signs and symptoms with the drug through the report of more similar cases. Correct diagnosis will spare the patient from unnecessary treatments.
What are the primary limitations to success in these cases?	■ To our knowledge, this is the first report of a possible oral side effect of PCSK9 inhibitors, therefore a comment on the primary limitations to success cannot be supported.

Acknowledgment

The authors report no conflicts of interest related to this case report.

CORRESPONDENCE
Grigoris Thermos, DDS, Private Practice, Kosti Palama 31, 11141 Athens, Greece.
E-mail: gthermos@dent.uoa.gr

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