

## **COVID-19 and oral cavity - repercussions and post-vaccination care: a clinical case**

**COVID-19 e cavidade oral - repercussões e cuidados pós vacinação: um caso clínico**

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### **Fernando Martins Baeder**

ORCID: <https://orcid.org/0000-0001-7101-5689>  
Cruzeiro do Sul University, Brazil  
E-mail: [fernandobaeder@uol.com.br](mailto:fernandobaeder@uol.com.br)

### **Lilian Aparecida Pasetti**

ORCID: <https://orcid.org/0000-0002-2392-4922>  
Primus Dentistry Institute, Brazil  
E-mail: [contato.primus.odontologia@gmail.com](mailto:contato.primus.odontologia@gmail.com)

### **Paola Fernanda Leal Corazza**

ORCID: <https://orcid.org/0000-0002-8639-8392>  
Metropolitan University of Santos, Brazil  
E-mail: [paola\\_corazza@hotmail.com](mailto:paola_corazza@hotmail.com)

### **Daniel Furtado Silva**

ORCID: <https://orcid.org/0000-0003-3319-2996>  
Federal University of Paraíba, Brazil  
E-mail: [furtado.ds@gmail.com](mailto:furtado.ds@gmail.com)

### **Ana Carolina Lyra de Albuquerque**

ORCID: <https://orcid.org/0000-0002-6532-5020>  
Federal University of Paraíba, Brazil  
E-mail: [lina.lyra@gmail.com](mailto:lina.lyra@gmail.com)

### **Dênis Clay Lopes dos Santos**

ORCID: <https://orcid.org/0000-0002-7321-235X>  
Cruzeiro do Sul University, Brazil  
E-mail: [denis.clay@cruzeirodosul.edu.br](mailto:denis.clay@cruzeirodosul.edu.br)

### **Antônio Francisco David**

ORCID: <https://orcid.org/0000-0002-5813-543X>  
Cruzeiro do Sul University, Brazil  
E-mail: [antonio.david@cruzeirodosul.edu.br](mailto:antonio.david@cruzeirodosul.edu.br)

### **Andreia Medeiros Rodrigues Cardoso**

ORCID: <https://orcid.org/0000-0002-2682-1048>  
Metropolitan Hospital Dom José Maria Pires, Brazil  
E-mail: [andreiamedeiros29@yahoo.com.br](mailto:andreiamedeiros29@yahoo.com.br)

### **Maria do Carmo Pessoa Nogueira Serrão**

ORCID: <https://orcid.org/0000-0002-0500-7485>  
Metropolitan Hospital Dom José Maria Pires, Brazil  
E-mail: [carminha11@hotmail.com](mailto:carminha11@hotmail.com)

### **Abstract**

Adverse event descriptions such as rare thromboses with concomitant thrombocytopenia, including venous thromboses at unusual sites such as cerebral venous sinus thrombosis (CVST), intestinal venous and arterial thromboses, have been reported following vaccination for COVID-19 based on recombinant adenoviral vector. The emergence of clinical features of moderate to severe thrombocytopenia and thrombotic complications, increasing fibrin formation in different parts of the body, approximately 1 to 2 weeks after vaccination against SARS-CoV-2 suggests a disorder that clinically resembles clinical presentations of long-term use of heparin. The case report consists of paroxysmal left-sided hemicrania after local vaccination protocol, in addition, the patient presents areas of retraction and papillary necrosis, hyperplastic regions with bleeding, not consistent with periodontal diseases associated with biofilm, during the physical examination. The possibility of ischemic stroke in vaccinated people as well as in patients with COVID-19 justifies the therapeutic and prophylactic use of anticoagulants, increasing post-vaccination safety. Although the phenomena related to thromboembolic complications induced by the vaccine for COVID-19 are rare, a careful evaluation including specific laboratory tests and a correct systemic diagnosis is necessary. In addition, the observation of certain pathologies caused by thrombus formation in the oral cavity can help in the preventive identification of vaccine-induced thrombotic thrombocytopenia (VITT).

**Keywords:** COVID-19; Vaccine; Anticoagulants; Thrombocytopenia.

## Resumo

Descrições de eventos adversos como tromboes raras com trombocitopenia concomitante, incluindo tromboes venosas em locais incomuns, como trombose do seio venoso cerebral (TSVC), tromboes venosas intestinais e arteriais, têm sido relatadas após vacinação para COVID-19 baseada em vetor adenoviral recombinante. O surgimento de quadros clínicos de trombocitopenia moderada a grave e complicações trombóticas, aumentando a formação de fibrina em diferentes partes do corpo, aproximadamente 1 a 2 semanas após a vacinação contra SARS-CoV-2 sugere um distúrbio que clinicamente se assemelha à quadros clínicos de utilização de heparina por longo período. O relato de caso consiste em quadro clínico de hemicrania paroxística esquerda após protocolo de vacinação local, além disso, a paciente apresentou áreas de retração e necrose papilar, regiões hiperplásicas com sangramento, não compatível com doenças periodontais associadas ao biofilme, durante o exame físico. A possibilidade de acidentes vasculares isquêmicos em pessoas vacinadas assim como em pacientes com COVID-19, justifica o uso terapêutico e profilático de anticoagulantes, aumentando a segurança pós vacina. Apesar de raros os fenômenos relacionados à complicações tromboembólicas induzidos pela vacina para COVID-19, é necessária uma avaliação cuidadosa incluindo exames laboratoriais específicos e um correto diagnóstico sistêmico. Além disso, a observação de determinadas patologias causadas por formação de trombos na cavidade oral podem auxiliar na identificação preventiva de trombocitopenia trombótica induzida pela vacina (TTIV).

**Palavras-chave:** COVID-19; Vacina; Anticoagulantes; Trombocitopenia.

## Resumen

Se han informado descripciones de eventos adversos como trombosis raras con trombocitopenia concomitante, incluidas trombosis venosas en sitios inusuales como trombosis del seno venoso cerebral (TSVC), trombosis venosa arterial e intestinal, después de la vacunación para COVID-19 basada en vector adenoviral recombinante. La aparición de características clínicas de trombocitopenia de moderada a grave y complicaciones trombóticas, que aumentan la formación de fibrina en diferentes partes del cuerpo, aproximadamente 1 a 2 semanas después de la vacunación contra el SARS-CoV-2, sugiere un trastorno que clínicamente se parece a las características clínicas del uso a largo plazo de heparina. El reporte de caso consta de cuadro clínico de hemicránea izquierda paroxística posterior a protocolo de vacunación local, además, al examen físico presentaba áreas de retracción y necrosis papilar, regiones hiperplásicas con sangrado, no compatible con enfermedades periodontales asociadas a biopelícula. La posibilidad de ictus isquémico tanto en personas vacunadas como en pacientes con COVID-19 justifica el uso terapéutico y profilático de anticoagulantes, aumentando la seguridad posvacunal. Aunque los fenómenos relacionados con las complicaciones tromboembólicas inducidas por la vacuna para la COVID-19 son raros, es necesaria una evaluación cuidadosa que incluya pruebas de laboratorio específicas y un correcto diagnóstico sistémico. Además, la observación de determinadas patologías provocadas por la formación de trombos en la cavidad oral puede ayudar en la identificación preventiva de la trombocitopenia trombótica inducida por vacunas (TTIV).

**Palabras clave:** COVID-19; Vacuna; Anticoagulantes; Trombocitopenia.

## 1. Introduction

Uncommon thrombotic events related to thrombocytopenias have been observed after vaccination with the recombinant adenoviral vector which encode the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein antigen (Corica et al., 2021; Dotan & Shoenfeld, 2021; Weber et al., 2021).

Several authors propose the occurrence of platelet activation resulting from the formation of adenovirus complexes, activated platelets, platelet factor 4 (PF4) and leukocytes. This union accelerates platelet clearance in the liver, clinically revealing a common thrombocytopenia after the administration of these vaccines. Serum samples obtained from several post-vaccination patients revealed the presence of active PF4 in the absence of heparin. In addition, patients also had moderate to severe thrombocytopenia after administration of adenoviral gene transfer vectors (McGonagle et al., 2021; Lavin et al., 2021).

Mechanisms of autoimmune thrombocytopenia similar to those induced by heparin have been described to explain the development of platelet activating antibodies and PF4 release after vaccination with recombinant adenoviral vector in patients without previous exposure to heparin (Corica et al., 2021; Dotan & Shoenfeld, 2021; Greinacher et al., 2021; McGonagle, De Marco & Bridgewood, 2021; Lavin et al., 2021; Weber von Hundelshausen & Siess, 2021).

Platelet activating antibodies bind to the complex formed by adenoviruses, activated platelets and PF4, activating intrinsic and extrinsic factors of the coagulation cascade to form fibrin, which increases the risk of thromboembolic

complications denominated vaccine-induced thrombotic thrombocytopenia (VITT) (Corica et al., 2021; Dotan & Shoenfeld, 2021; Greinacher et al., 2021; McGonagle et al., 2021; Lavin et al., 2021; Weber et al., 2021).

The objective of this work is to present a clinical case with a possible relationship between VITT with the vaccine for the prevention of SARS-COV-2, and some lesions and oral manifestations in order to assist health professionals in the diagnosis to contribute to the appropriate management of these patients.

## 2. Methodology

The present study consists of a case report developed with the collaboration of dentists and neurologists from different institutions. The study was submitted and approved by the research ethics committee, under protocol CAAE 45065721.6.0000.8447. The participant in this study agreed to the Free and Informed Consent Term, respecting the ethical principles of the Declaration of Helsinki (Pereira et al., 2018).

## 3. Case Report

Female caucasian patient with 49 years old had administered the 1st dose of recombinant adenoviral vector encoding spike protein antigen vaccine on 02/03/2021, without experiencing any adverse reaction. Respecting local vaccination protocol, the 2nd dose of recombinant adenoviral vector vaccine was administered at 05/03/2021. Seven days after the second dose, the patient had paroxysmal left-sided hemicrania, diagnosed as Arnolf's Neuritis, or Greater and Lesser Occipital Neuralgia. Three days after the onset of symptoms, the patient underwent RT-PCR test for COVID-19, with a negative result.

After clinical evaluation by a neurologist, investigational post-vaccination COVID-19 tests were ordered. The tests requested were: Laboratory tests (coagulogram, blood count, D-dimer, lupus anticoagulant, anticardiolipin antibody) and cerebral cavernous sinus angiogram. The results of laboratory tests were normal, with the exception of D-dimer which 1.36 mcg/ml. Clinical protocols indicate that patients with D-dimer laboratory tests above 1.0 mcg/ml have had a worse clinical evolution and should use preventive anticoagulants, moreover those above 1.50 mcg/ml require hospital care (Terpos et al., 2020).

The patient required dental care complaining of pain and bleeding in certain regions, during the period in which she had a D-dimer with values of 1.36 mcg/ml. The clinical signs found were: areas of retraction and papillary necrosis (Figure 1), hyperplastic regions with bleeding, not consistent with periodontal diseases associated with biofilm, during the physical examination, the patient presented a depapilated tongue with burning sensation (Baeder et al., 2021a; Baeder et al., 2021b; Papanou et al., 2018).

**Figure 1.** Initial appearance of the gingival papilla prior to anticoagulant treatment (black arrow).



Source: Own authorship.

In view of the alterations presented in the oral cavity, and articles related to possible formation of thrombi, the dental surgeon referred the patient to the hematologist, who requested, in addition to the existing exams, echo Doppler of the lower limbs, such as investigation of thrombosis and varicose veins pre-vaccination, which the result was negative. Once the vaccine reaction was confirmed, the hematologist prescribed a common preventive anticoagulant (daily 10 mg of rivaroxaban for continuous use) used in protocols for vaccine reactions against COVID-19 (Payares-Herrera et al., 2021).

In the period of thirty days in which the patient is anticoagulated, she sought the dentist again. Control by tests related to anticoagulation revealed a D-dimer with a result of 0.96 mcg/ml. The physical examination of the oral cavity revealed normality in the gingiva region without necrotic or hyperplastic areas, and the disappearance of depapillated areas with no pain on the dorsum of the tongue was observed.

**Figure 2.** Appearance of the gingival papilla after 3 weeks of anticoagulant treatment (black arrow).



Source: Own authorship.

#### 4. Discussion

Clinical features of moderate to severe thrombocytopenia and thrombotic complications, increasing fibrin formation in different parts of the body, starting approximately 1 to 2 weeks after vaccination against SARS-CoV-2 with recombinant adenoviral vector suggests a disorder that clinically resembles patients who developed thrombocytopenia from long-term heparin use (Greinacher et al., 2021).

Induced thrombocytopenia is a known prothrombotic disorder, caused by heparin-induced platelet activating antibodies, forming associated protein complexes or macromolecules activating factor PF4 and clotting factors, increasing the amount of fibrin polymers, facilitating the formation of thrombi or emboli. However, contrary to the usual situation in heparin-induced thrombocytopenia, patients vaccinated, mainly with recombinant adenoviral vector and who do not receive heparin, develop occurrences of thrombosis and thrombocytopenia (Corica et al., 2021; Dotan & Shoenfeld, 2021; Greinacher et al., 2021; McGonagle et al., 2021; Lavin et al., 2021; Weber von Hundelshausen & Siess, 2021).

The COVID-19 vaccine based on recombinant adenoviral vector encoding the spike glycoprotein SARS-CoV-2 revealed rare thromboses with concomitant thrombocytopenia, including venous thromboses in uncommon sites such as cerebral venous sinus thrombosis (CVST), intestinal venous and arterial thromboses (Gürtler et al., 2021).

This clinical case reveals symptoms similar to possible thrombotic events that may clarify the patient to have developed paroxysmal hemicrania on the left side, diagnosed as Arnold's Neuritis, or Greater and Minor Occipital Neuralgia, 7

days after the administration of recombinant adenoviral vector vaccine second dose. The diagnosis of Greater and Lesser Occipital Neuralgia may be associated with ischemic processes due to the increase in fibrin polymers forming thrombi and producing ischemic processes (Xiong et al., 2020).

These clinical features that resemble those of heparin-induced autoimmune thrombocytopenia, thereby activating clotting processes and fibrin clot formation, were observed in patients with vaccine-induced immune thrombotic thrombocytopenia, including several patients with cerebral venous thrombosis (CVT) induced by the vaccine with the recombinant adenoviral vector (de Simone et al., 2021).

In laboratory tests, the patient had D-dimer with values of 1.36 mcg/ml, this result reinforces the clinical case published by Li et al. (2020). Which related a 54-year-old female patient presented with characteristic signs and symptoms (elevated D-dimer 1.46 mcg/ml).

According to Rostami & Mansouritorghabeh (2020) in a systematic review, the authors found an elevation of D-dimer in 36-43% of COVID-19 cases, with a correlation between higher D-dimer values and more severe cases of the disease. Platelet activating antibodies bind to the adenovirus-activated platelet complex and PF4, activating intrinsic and extrinsic factors of the coagulation cascade, forming fibrin and increasing the possibility of VITT (Corica et al., 2021; Dotan & Shoefeld, 2021; Greinacher et al., 2021; McGonagle et al., 2021; Lavin et al., 2021; Weber von Hundelshausen & Siess, 2021).

These studies reinforce the possibilities of ischemic vascular accidents in vaccinated people as in patients with covid-19, which justifies the therapeutic and prophylactic use of anticoagulants, increasing post-vaccination safety (Fu et al., 2020; Moreno et al., 2021).

In periodontics, papillary necrosis may be related to local or systemic factors, respectively, such as lack of blood supply, infection and excessive manipulation of tissues or physiological factors, stress, immunity, nutrition, hormonal situation (Nikoloudaki et al., 2020; Pitones-Rubio et al., 2020; Cho et al., 2021).

According to Cho et al. (2021) and Nikoloudaki et al. (2020) after tissue necrosis due to lack of blood supply and if adjacent tissues are preserved and a possible revascularization exists, the tissue is restored in a preserved way. These studies justify why, after the use of anticoagulants, the patient reestablished her periodontal condition.

## 5. Final Considerations

Although the phenomena related to thromboembolic complications induced by the vaccine for COVID-19 are rare, they can occur, so a careful evaluation including specific laboratory tests and a correct systemic diagnosis including certain pathologies caused by thrombus formation in the oral cavity can help in the preventive identification of VITT. Thus, preventive measures for potentially lethal thromboprophylaxis will likely reduce the overall mortality rate. In addition, these findings reveal the need for a more accurate investigation into the possible risks that may arise with the administration of some vaccine protocols for COVID-19.

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