



Case Report

An Adverse Effect of Ocrelizumab Treatment in a Patient with Multiple Sclerosis: A Case Report of Necrotizing Periodontitis

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Abstract

Multiple Sclerosis (MS) and Necrotizing Periodontitis (NP) are two diseases whose aetiologies and pathophysiologies do not appear to have a common link; however, treating MS with monoclonal antibodies and the decrease in humoral immunity that this entails can be a trigger or an aggravation in patients who present with quiescent NP. We describe a clinical case of NP, including clinical manifestations, treatment, and evolution during therapy with ocrelizumab and to review risk factors. A rapid progression of NP was evidenced. During the patient's evolution, she suffered bilateral pneumonia due to coronavirus disease 2019, requiring treatment with corticosteroids and antibiotics, which led to clinical relief of her NP. Based on this case, we believe that regulated dental monitoring of patients with MS before, during, and after the administration of monoclonal antibodies may help prevent periodontal deterioration.

Keywords: Multiple Sclerosis; Necrotizing Periodontitis; Periodontal Disease; Periodontal Treatment; Periodontitis; Relapsing-Remitting Multiple Sclerosis

Introduction

Multiple Sclerosis (MS) is an inflammatory neurodegenerative autoimmune disease of the Central Nervous System (CNS). Over the past 20 years, the treatment scenario for MS has changed dramatically. Immunomodulators and immunosuppressants are used to treat MS. Ocrelizumab is a humanized monoclonal antibody against the CD20 antigen of B cells, and among its side effects, a substantial increase in infections has been described [1].

Necrotizing Periodontitis (NP) is a periodontal infection that causes necrosis and ulceration of the interdental papilla, gingival bleeding, pain, pseudomembrane formation, halitosis, loss of periodontal attachment, and bone destruction [2]. It is an infectious condition with predisposing factors in which the host's

immune response plays a fundamental role [3].

Here, we describe a rare complication of ocrelizumab treatment for MS, during which several outbreaks of NP occurred.

Case Report

A 28-year-old woman was consulted by telephone during the COVID-19 lockdown period in Spain (March–May 2020). She reported intense and persistent pain of the gingiva with spontaneous bleeding and halitosis, as well as generalized discomfort. The patient did not want to physically come to the office for fear of coronavirus 2019 (COVID-19) infection. The patient appeared to be under significant emotional stress. Her medical history included relapsing-remitting MS (RR-MS), diagnosed in 2018. She had been treated with monoclonal antibodies (ocrelizumab) since November 2019 (600 mg, administered by intravenous infusion every 6 months). She smoked ten cigarettes per day and was a social drinker on weekends. She also had an allergy to coconut and used

a night guard due to bruxism. Under the presumptive diagnosis of necrotizing gingivitis, treatment with hygiene improvement and 0.12% chlorhexidine rinses every 8 h after brushing was advised. As a result, the patient reported relief of symptoms within a few days without disappearing completely.

After the COVID-19 lockdown ended (May 2020), the patient was sent to her general dentist. She had no current complaints, and a panoramic radiograph was ordered (Figure 1a). She received professional oral hygiene, with symptoms diminishing.

In November 2020, the patient was administered a new dose of ocrelizumab, and a few weeks later, she reported a new outbreak of intense gingival pain accompanied by interdental papilla loss. The patient decided to reinstate treatment with improved oral hygiene and 0.12% chlorhexidine rinses thrice daily. The patient reported that again, the symptoms improved almost completely.

In April 2021, her general practitioner performed routine cytometry. The CD19/CD20+ B lymphocyte population was 0%, with cellular immunity preserved. This percentage reflected deeper humoral immunosuppression (normal values 3%–10%). These data indicated, on the one hand, the effectiveness of the treatment and, on the other hand, the predisposition to bacterial infections.

In May 2021, due to the persistence and severity of the oral symptoms, her general practitioner referred the patient to our unit for study and treatment. A complete examination included oral photography, panoramic radiography (Figure 1b), and periodontogram. Remarkably, the patient presented pathologic tooth migration due to lingual thrust. The study of her occlusion was within the limits of normality. The patient reported acute pain, and exploration showed insertion loss and recessions in the upper and lower incisors. The patient reported being very worried and stressed by the oral discomfort and progressive loss of aesthetics of her teeth. However, at this time, she was stabilized (Figures 2a and 3a).

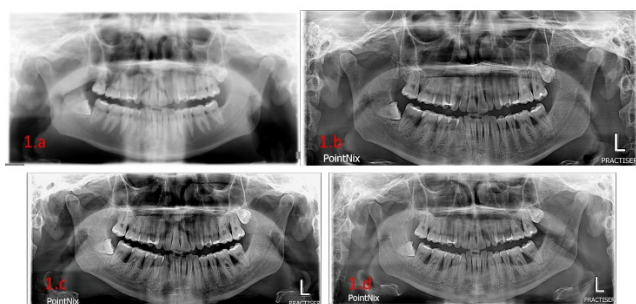


Figure 1: Sequence of Panoramic radiographs (OPTs).1a. Initial OPT performed by the patient's general dentist in May 2020. The bone levels are preserved and located 1.5 mm from the amelocemental limit. The inclusion of the 2.8 and 4.8 (wisdom

teeth) is appreciated. 1b. OPT performed in May 2021 (1 year later) shows predominantly vertical loss at the level of molars and incisors. 1c. OPT in September 2021, the pattern of bone loss changed to very prominent horizontal bone loss at the level of the upper and lower molars. 1d. Final OPT in January 2022 shows a large horizontal bone loss with a distance to the amelocemental boundary of 5 mm at the molar level.



Figure 2: Clinical photographs of the frontal view of the patient.2a. In May 2021, during his first visit to our unit and 1 year after the onset of the first outbreak. The gingiva's inflammation and the interproximal papillae' decapitation can be seen. 2b. In January 2022, the patient had good gingival colouration, but plaque control and chlorhexidine stains were visible. The patient had loss of papillae and generalized recession.



Figure 3: Right lateral photograph.3a. In May 2021, the patient's first visit to our unit. There is a slight loss of the mesial papilla of 46 and 13 with inflammation of the gingiva of the lower incisors. 3b. In January 2022, the patient lost both the mesial and distal papillae of the right lower first molar, although the bifurcation of the molar remained closed.

Due to the persistence of NP, a microbiological study was performed to determine the presence of particularly aggressive bacteria and focus on possible antibiotic treatment. As a result, both *Tannerella forsythia* and *Prevotella intermedia* were detected (Table 1).

Bacteria	Number	Degree of periopathogenesis
<i>Aggregatibacter actinomycetemcomitans</i> (Aa)	0	Absent
<i>Tannerella forsythia</i> (Tf)	538,954	High
<i>Porphyromonas gingivalis</i> (Pg)	0	Absent
<i>Treponema denticola</i> (Td)	0	Absent
<i>Prevotella intermedia</i> (Pi)	473,945,362	High
<i>Campylobacter rectus</i> (Cr)	0	Absent

Table 1: Microbiological examination results. Notably, *Prevotella intermedia* and *Tannerella forsythia* were present.

On the recommendations of her neurologist, because she was scheduled to receive a new dose of ocrelizumab, periodontal treatment was postponed for 4–6 weeks due to possible immunosuppression. However, 10 days after the administration of ocrelizumab, a new outbreak of severe gingival pain was reported. She showed ulcerative lesions in 3.6 and 3.7 (Figure 4). During this time, the patient began a smoking cessation program. Mouthwash

with 0.12% every 8 h of chlorhexidine digluconate, reinforcement of hygiene techniques, and oral irrigators were prescribed.



Figure 4: Lateral clinical photograph at the lingual level of the lower left first molar (3.6) in May 2021 during the patient’s initial visit to our unit. The loss of both mesial and distal papillae with a large crater at the distal aspect was observed. The patient reported intense pain that made exploration difficult.

In June 2021, periodontal treatment (for hemiarches) was resumed. The rinses were maintained with 0.12% chlorhexidine digluconate every 12 h, followed by panthenol, cetylpyridinium chloride, and zinc lactate.

A new periodontogram was performed. The data are summarized in Table 2.

	Mean probing depth	Mean insertion level	Plaque index	Bleeding index
May 2021	4.93 mm	5.68 mm	7%	25%
July 2021	3.74 mm	4.64 mm	2%	7%
September 2021	2.98 mm	4.72 mm	2%	3%
January 2022	2.95 mm	3.55 mm	8%	3%

Table 2: Summary of periodontal data.

In September 2021, the patient presented with a new outbreak of pain in the lower molar area. After the second COVID-19 vaccine (Pfizer) dose, she suffered a pseudo-outbreak of MS with loss of vision in the left eye and paraesthesia in the left hand lasting less than 24 h. The patient reported neglecting her healthy lifestyle during the summer, with less oral hygiene and greater social activity. Tooth polishing was performed with a brush and prophylaxis paste and rinsed with 0.12% chlorhexidine digluconate.

Fifteen days later (September 2021), a new periodontogram and panoramic radiograph were performed (Figure 1c), which detected greater bone loss in the areas of 2.6–2.7, 3.6–3.7, and 4.6–4.7 compared to the one performed 5 months earlier.

One week later, the patient presented with a new outbreak of gingiva. During this time, the patient commented that she had been under great stress with irregular rest periods.

On November 19, she received a new dose of ocrelizumab. Although the patient had received a third dose of the COVID-19 vaccine, she exhibited COVID-19 symptoms, and on Day 24, a positive diagnosis of COVID-19 was confirmed. On December 7, there was a worsening associated with the onset of fever (38.5°), chills, and dyspnoea. The patient was hospitalized following a diagnosis of bilateral pneumonia due to COVID-19 in an immunocompromised patient. She was treated with azithromycin 500 mg, methylprednisolone, oxygen, and nonsteroidal anti-inflammatory drugs (NSAIDs) and was discharged on January 5, 2022.

In January 2022, the patient’s gingiva had a coral-pink colour with orange peel stippling due to the absence of oedema and ulcerative gingival lesions, which were compatible with gingival health. New intraoral photographs were taken, a new periodontogram and panoramic radiograph were performed, and a periodontal maintenance session was conducted (Figures 1d, 2b

and 3b).

In March 2022, the patient was again diagnosed with COVID-19. She had mild symptoms and was treated with three doses of remdesivir. A few days after being discharged, a new periodontal review was performed, the results of which were similar to those of the previous exam.

Discussion

MS progresses in an unpredictable manner, manifesting symptoms that vary from person to person [4]. Classically, MS has been considered a T-lymphocyte-mediated disease. However, the role of B lymphocytes has been speculated for decades. It is now known that activated B-lymphocyte-derived plasmablasts can remain in the cerebrospinal fluid of MS patients for very long periods.

The medication used for its treatment (immunomodulators) and to alleviate its symptoms (corticosteroids) can have effects on the oral mucosa (xerostomia, gingival hyperplasia, mucositis, aphthae, dysgeusia, candidiasis or angular cheilitis), which potentially contributes to worse oral health [5]. Cockburn et al. [6] indicated that up to 18 oral problems related to these drugs had been described, in addition to favouring the appearance of opportunistic infections.

Ocrelizumab is an IgG1 monoclonal antibody that selectively targets CD20+. The treatment causes a rapid decrease in circulating B cells and immunoglobulin levels without affecting lymphoid stem cells or plasma cells. Its effect was observed after 14 days, with a significant decrease in B lymphocytes (CD19+) in the lymph nodes. Measurement of CD19+ cells by flow cytometry is a surrogate measure of B lymphocytes in patients treated with anti-CD20 antibodies. Its effects persist between 6 and 18 months after the last dose.

Ocrelizumab has been studied in two pivotal clinical trials for relapsing MS: OPERA I and OPERA II. In both trials, ocrelizumab significantly reduced the rate of relapses and the progression of disability compared to an injectable disease-modifying therapy. Additionally, ocrelizumab significantly reduced the number of new or enlarging lesions on MRI scans compared to interferon beta-1a.

Overall, ocrelizumab has been shown to be an effective treatment for relapsing MS, with a significant reduction in relapses and disability progression. It is approved for treating both relapsing forms of MS and primary progressive MS.

In the case of periodontitis, it has been suggested that because both MS and periodontitis have an immune component, there could be some association between both diseases. However, Gustavsen et al. [7] indicated no significant association between MS and periodontitis after adjusting for smoking habits in their study. Sheu and Lin [8] found evidence of this association among women but not men.

Necrotizing periodontal diseases (NPDs) are characterized by the following main features: pain, necrosis of the papillae, and gingival bleeding [9].

Although their prevalence is low, NPDs importance lies in the severity and progression of the disease. Its aetiology is influenced by several factors that can condition the host's response to the disease. These include immunodeficiencies, malnutrition, stress, and smoking. In addition to these factors, a specific bacterial association has been established, classically as a fusio-spirillary association [10].

Our patient had several predisposing factors, including immunosuppression, stress, smoking, poor oral hygiene, late periodontal treatment, and characteristic bacterial flora. Focusing on the factors present in the patient, we highlight significant contributing aspects below.

Immunosuppression Factor

As shown by April 2021 cytometry, the CD19/CD20+ B lymphocyte population was 0%, indicating effective humoral immunosuppression. We do not know if her humoral immunosuppression was maintained throughout the evolution of the case since the rest of the analyses were focused on the evaluation of T lymphocyte subpopulations (CD3+).

The patient also had 2 COVID-19 infections. The novel coronavirus (COVID-19) has been linked to an increased risk of exacerbation of MS symptoms. This is likely due to the fact that the virus causes inflammation and can affect the immune system. In people with MS, this can lead to a flare-up of symptoms or an exacerbation of existing disease. Additionally, people with MS are more susceptible to infections and may be more likely to contract COVID-19. Those with MS should take extra precautions to protect themselves, such as wearing a face mask, washing their hands frequently, and avoiding large gatherings.

Stress Factor

It is known that psychological stress affects human immune function [11]. For some authors, the combination of both periods of psychological stress and situations of immunosuppression are predisposing factors for the worsening of the disease [6,11], which leads to an increased risk of infections or their progression. These interconnections might be even more relevant in recurrent and aggressive cases of periodontal and peri-implant disease, often refractory to treatment [12].

Burtscher et al. [13] found that the isolation of people, in combination with the fear of contagion and quarantine, as well as a possible information overload, caused chronic stress and was associated with adverse effects on mental health.

Smoking Factor

It has been known for years that tobacco is the most important

acquired risk factor in the treatment and prognosis of periodontal diseases [14]. Its content in various chemical products alters the inflammatory response, resulting in a potent toxicant for various cell types [15]. It should be noted that nicotine releases catecholamines both locally and systemically, which alters the vascular flow at the level of the gingival papillae, favouring papillary necrosis and increasing periodontal destruction [16].

In the present case, the patient was a smoker and did not begin treatment for smoking cessation until near the end of her evolution. This situation could have hindered treatment and favoured her relapses.

Poor oral Hygiene

The physical sequelae and the progressive deterioration produced by MS may imply greater difficulty in performing proper oral hygiene or accessing adequate oral care. Moreover, studies have demonstrated that smokers have higher plaque levels, more pathogenic flora, and less favourable responses to periodontal treatment [17].

Hatipoglu et al. [18] found higher values of the plaque index, probing depth, and gingival index in MS patients among patients with high levels of physical disability than among patients with low levels of disability.

Late Periodontal Treatment

Early diagnosis and prompt treatment of the disease prevents progression and cellular destruction and results in disease resolution [19].

The delay in treatment due to confinement and the fear of going to a dental office allowed subclinical evolution, with false periods of remission.

Microbiological Factor

It has been described that the rate of infections (mainly upper respiratory tract) is estimated at 75.6 per 100 patient-years (CI 95%: 73–78.2), although fortunately, the accumulated rate of severe infections in all the clinical trials was 1.3% for ocrelizumab [20].

NP is an opportunistic bacterial infection predominantly associated with *Treponema* spp., *Selenomonas* spp., *Fusobacterium* spp., and *Prevotella intermedia*. In our case, the predominant bacteria were *Tannerella forsythia* and *Prevotella intermedia* (Table 1).

According to the summary of the product characteristics of ocrelizumab and following its mechanism of action, inoculation with live or live attenuated vaccines is not recommended during treatment until B-cell repletion [20,21]. However, we have no information on mRNA-based vaccines.

To our knowledge, this is the first study to describe NP during RR-MS treatment. We found that NP is linked to treatment

with immunomodulators, which cause a substantial decrease in humoral immunity. This case highlights the need for an oral care protocol for patients who undergo immunomodulation.

Conclusion

Given the possible relationship between the immunomodulation of patients affected by RR-MS and the risk of presenting with NP, we recommend an evaluation and dental follow-up of patients with MS before, during, and after the administration of monoclonal antibodies.

We make three final recommendations to consider when elaborating on the general treatment regimen for NPDs: (A) early treatment often prevents sequelae and craters in soft tissues that will have new relapses; (B) treatment must be maintained even though the pain has disappeared following the application of the emergency measures; if not, relapses will occur more often; and (C) we must consider that a patient can fail to respond to this treatment, especially with advanced degrees of immunodepression.

Author Contributions:

Conceptualization, A.S.-P. and J.M.M.-C. ; methodology, A.S.-P. and A.J.-G. ; investigation, J.M.M.-C. and A.S.-P.; data curation, M.J.M.-V. and A.J.-G. ; writing—original draft preparation, J.M.M.-C. ; writing—review and editing, A.S.-P., A.J.-G., J.M.M.-C., M.J.M.V., and J.M.M.C. ; A.S.-P., supervision, and J.M.M.-C.

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