

Phototherapies in the management of an ulcerative lip lesion in a patient taking multiple medications for rheumatoid arthritis

Fototerapias no tratamento de lesão ulcerativa labial em paciente recebendo diversos medicamentos para artrite reumatóide

Fototerapias para el manejo de una lesión labial ulcerosa en un paciente en tratamiento con múltiples medicamentos para la artritis reumatoide

Received: 06/24/2021 | Reviewed: 07/01/2021 | Accept: 07/06/2021 | Published: 07/09/2021

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Abstract

The treatment of rheumatoid arthritis (RA), an inflammatory autoimmune disease of chronic nature, consists of medications, exercises, patient education on the disease, and rest. Unfortunately, many drugs used for RA have been recently recognized to induce oral manifestations due to either immunosuppression or antiproliferative effects. Thus, the present study reports a case of a patient who was receiving multiple medications (methotrexate, leflunomide, and sodium risedronate) for RA and developed an extensive lip ulcerative lesion not responsive to previous treatments. The lesion management was performed using only a combination of photobiomodulation therapy (PBMT) and antimicrobial photodynamic therapy (aPDT), totalizing three laser sessions. Within 4 days, the patient no longer complained of pain and the lesion presented an advanced healing aspect. According to the current case, the combination of PBMT and aPDT seems to be a suitable alternative for the management of oral lesions in patients taking medications for RA.

Keywords: Photochemotherapy; Low-level light therapy; Rheumatoid arthritis; Oral ulcer; Lip diseases.

Resumo

O tratamento da artrite reumatoide (AR), uma doença inflamatória autoimune de natureza crônica, consiste em medicamentos, exercícios, instrução ao paciente sobre a doença e repouso. Infelizmente, muitos medicamentos utilizados para AR recentemente foram associados a manifestações orais por imunossupressão ou efeitos antiproliferativos. Assim, o presente estudo relata o caso de um paciente que estava recebendo vários medicamentos (metotrexato, leflunomida e risedronato de sódio) para AR e desenvolveu uma lesão ulcerativa labial extensa não responsiva a tratamentos prévios. O manejo da lesão foi realizado apenas com a combinação de terapia de fotobiomodulação e terapia fotodinâmica antimicrobiana, totalizando três sessões de laser. Em 4 dias, a paciente não se queixava mais de dor e a lesão apresentava aspecto de cicatrização avançado. De acordo com o caso atual, a

combinação de terapia de fotobiomodulação e terapia fotodinâmica antimicrobiana parece ser uma alternativa adequada para o manejo de lesões orais em pacientes em uso de medicamentos para AR.

Palavras-chave: Fotoquimioterapia; Terapia com luz de baixa intensidade; Artrite reumatóide; Úlcera oral; Doenças labiais.

Resumen

La artritis reumatoide (AR) es una enfermedad inflamatoria autoinmune de naturaleza crónica, cuyo tratamiento consiste en medicamentos, ejercicios y en educar al paciente sobre la enfermedad y el reposo necesario. Sin embargo, se ha reconocido recientemente que muchos fármacos utilizados para tratar la AR ocasionan manifestaciones orales debido a sus efectos inmunosupresores o antiproliferativos. El presente estudio reporta el caso de un paciente que estaba recibiendo múltiples medicamentos (metotrexato, leflunomida y risedronato de sodio) para la AR y desarrolló una lesión ulcerosa labial extensa que no respondió a tratamientos previos. Se optó por una combinación de terapia de fotobiomodulación y terapia fotodinámica antimicrobiana, totalizando tres sesiones de láser. A los 4 días, el paciente ya no se quejaba de dolor y la lesión presentaba aspecto de cicatrización avanzado. Los resultados sugieren que la combinación de terapia de fotobiomodulación y terapia fotodinámica antimicrobiana parece ser una alternativa adecuada para el manejo de lesiones orales en pacientes que utilizan medicamentos para tratar la AR.

Palabras clave: Fotoquimioterapia; Terapia por luz de baja intensidad; Artritis reumatoide; Úlceras Bucales; Enfermedades de los labios.

1. Introduction

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease of chronic nature that affects small joints at first and progresses further to larger joints, resulting in severe pain. The treatment of RA aims to mitigate joint inflammation and pain, improve joint function, and prevent further destruction and deformity, and is based on combinations of medications, exercises, patient education on the disease, and rest (Bullock et al., 2019).

Commonly based on immunosuppressants and anti-resorptive agents, drug therapy regimens for RA vary widely in the literature, each one presenting its pros and cons such as deleterious oral repercussion. Methotrexate is general used as second-line therapy for RA because of anti-inflammatory and immunosuppressive effects but important oral alterations are commonly seen (Pedrazas et al., 2010). Leflunomide, a member of the disease modifying antirheumatic drugs group with immunosuppressive, antiproliferative, and anti-inflammatory properties, seems also to be capable of affecting the oral cavity (Kalogirou et al., 2017). Likewise, although bisphosphonates are effective in preventing generalized bone loss and focal bone damage in RA patients (Breuil & Euller-Ziegler, 2006), some studies have been suggested that they are related to oral manifestations thanks to the antiproliferative and pro-apoptotic cytotoxic effects on epithelial cells (Lengfeld et al., 2016).

Low-level laser therapeutic modalities such as antimicrobial photodynamic therapy (aPDT) and photobiomodulation therapy (PBMT) have been gaining attention recently for the treatment of many oral conditions in immunocompromised patients given that their general medical characteristics require very special care and the clinical response to conventional measures may be unpredictable (Rezende et al., 2020; Campos et al., 2021; Mosca et al., 2021). In light of these facts, the present study aims to report a clinical case in which these phototherapies were used for the management of a lip ulcerative lesion in a patient taking multiple medications for RA.

2. Case Report

An 83-year-old female was admitted at Charity Hospital of Campo Grande (MS, Brazil) because of a whitish lesion throughout her lower lip and difficulty in performing normal oral functions that had arisen approximately 7 days ago. Just after the initiation of the symptoms, she had sought medical help in a basic health unit and topical agents (triamcinolone acetonide, acyclovir, nystatin, and hydrogen peroxide) had been prescribed for 5 days; however, there had been no clinical improvement.

The patient also suffering from systemic arterial hypertension, dyslipidemia, digestive complaints, rheumatoid arthritis, Parkinson's disease, depression, and anxiety. So, she was receiving many medications and dietary supplements as

follows: losartan, hydrochlorothiazide, dexlansoprazole, leflunomide, citalopram, levodopa and benserazide hydrochloride, simvastatin, vitamin D, omega-3, amitriptyline and chlordiazepoxide, sodium risedronate, methotrexate, and *Cynara scolymus* L. extract.

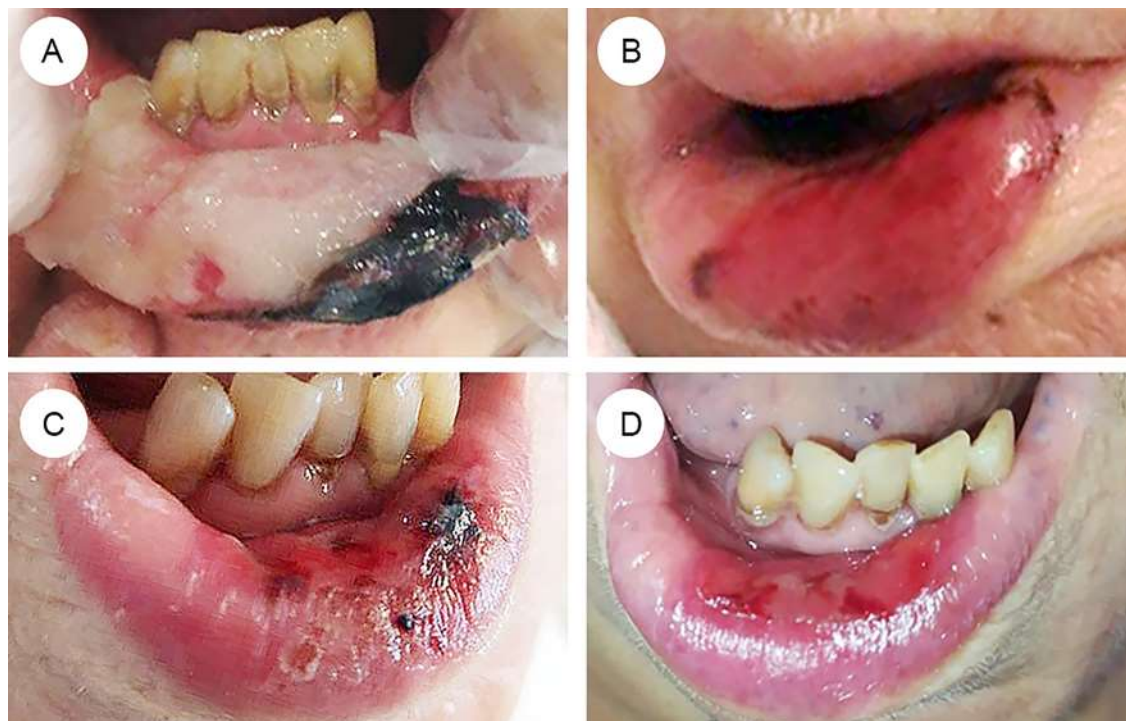
The complete blood count revealed pancytopenia and hyponatremia, the main reasons for hospitalization on the same day. Intraoral physical examination showed whitish lesions throughout the oral cavity and a hyperemic lesion with yellowish secretion on the lower lip. To rule out fungal infection on some intraoral areas, topical nystatin and systemic fluconazole were then prescribed and platelet transfusion was performed. A nasogastric tube was also used for feeding since the patient reported severe pain on the lesions, that compromised an oral food intake.

On the third day, almost no clinical improvement was achieved. Considering a possible bacterial infection, imipenem was administered and both methotrexate and leflunomide were discontinued. On the fourth day, folic acid was prescribed and oxygen therapy with a nasal catheter was proposed due to low oxygen saturation (89%). On the sixth day, despite total remission of the intraoral whitish lesions, the lesion affecting the lower lip got worse and became covered by a thick hemorrhagic and fibrinous layer (Figure 1A).

According to these clinical aspects, all antimicrobials were discontinued and both chlorhexidine and dexamethasone mouthrinses were prescribed. Besides supportive oral care measures, an aPDT session was performed. For that, 0.01 % methylene blue was applied over the lesion and, after 5 min (time pre-irradiation), the laser Therapy EC® (DMC, São Carlos, SP, Brazil) was used at 660 nm, on contact mode, with 100 mW, 35 J/cm², 5 J, and 50 s. Moreover, two PBMT sessions were carried out with a 24-hours interval on the same area previously described (5 points) and using the same equipment, but applying 100 mW, 35 J/cm², 2 J, and 20 s of irradiation per point (Figure 1B). The protocols were based on other studies (Campos et al., 2020; Rezende et al., 2020; Ramires et al., 2021).

After 24 hours from the first laser application, the lip lesion presented an important improvement in healing (Figure 1C). Within further 48 hours, the patient no longer complained of oral pain and then the reinstatement of oral food intake was possible (Figure 1D). Clinical care measures were maintained for only two more days, until hospital discharge.

Figure 1. Clinical evaluation of a case of an ulcerative lip lesion in a patient taking multiple medications for rheumatoid arthritis treated with phototherapies.



A) Initial presentation of the extensive ulcer with crust on the lower lip which had been not responsive to previous treatment attempts; (B) The clinical features immediately after cleaning the lesion and before a laser session; (C) 24 hours after the laser irradiation, showing great improvement in the healing process; (D) Last laser session, showing an advanced stage of healing.
Source: Authors.

3. Discussion

In the current case report, aPDT and PBMT resulted in an important clinical improvement of the patient's oral condition related to the lip lesion within approximately three days. To the best of the authors' knowledge, this is the first study on the benefits of this phototherapeutic approach to a RA patient receiving multiple medications known to have an impact on the oral tissues.

From the clinical point of view and considering the patient's medical history, some diagnostic hypotheses were formulated since the lip lesion was not responsive to previous treatment attempts. One relies on the immunosuppression status induced by methotrexate (Pedrazas et al., 2010) and leflunomide and another on the antiproliferative effects achieved by leflunomide (Kalogirou et al., 2017) and sodium risedronate (Lengfeld et al., 2016). In fact, the authors strongly believe in a synergistic effect of all these drugs, the reason for combining aPDT and PBMT (Rezende et al., 2020; Campos et al., 2021; Rezende et al., 2021).

Used in clinical practice for more than 60 years by now, there are several well-documented effects of PBMT, which are based on a process initiated from the absorption of laser light by mitochondrial chromophores, and favors pain relief, inflammatory modulation, and tissue healing (Karu, 2010; Masha et al., 2013). Especially, irradiation with red light (660 nm) has been the best choice for collagen production, healing-resistant wounds, and ulcers, due to its absorption by the most superficial cell layers of the organism (Karu, 2010; Masha et al., 2013). In addition, its wavelength, when associated with the resonant photosensitizing agent, promotes the generation of reactive oxygen species and consequent antimicrobial effect,

playing a fundamental role against bacterial, viral, and fungal coinfections without influence on both microbial resistance and selection (Pérez-Laguna et al., 2018; Peralta-Mamani et al., 2019).

4. Final Considerations

The combination of phototherapies herein applied seems to be a safe and suitable therapeutic modality for oral lesions related to medications used in RA treatment, promoting immediate analgesia and tissue repair. However, the use of phototherapies in polypharmacy patients is still incipient and warrants further research with well-controlled studies.

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