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Case report

Infliximab is effective in difficult-to-control peripheral ulcerative keratitis. A report of three cases☆

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ABSTRACT

Peripheral ulcerative keratitis is caused by an inflammatory and destructive process of the perilimbal peripheral cornea. This inflammation is due to immune complex deposition in this region of the cornea and in adjacent vessels. It can be idiopathic, or a manifestation of systemic disease such as rheumatoid arthritis, vasculitis of small vessels associated with ANCA, relapsing polychondritis, systemic lupus erythematosus and Crohn's disease. Its treatment includes the use of high-dose corticosteroids and, in some cases, the concomitant use of immunosuppressants such as methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide or cyclosporine. The use of immunobiological agents can be a strategy in cases of difficult control. The authors describe the treatment of three patients who, after failure with the use of corticosteroids or immunosuppressants, showed good response after the use of infliximab.

Infliximabe é eficaz em ceratite ulcerada periférica de difícil controle. Um relato de três casos

Palavras-chave:
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RESUMO

Ceratite ulcerada periférica é causada por um processo inflamatório e destrutivo da córnea periférica perilimbar. Essa inflamação se deve à deposição de imunocomplexos nessa região da córnea e nos vasos adjacentes a ela. Pode ser idiopática ou uma manifestação de doença sistêmica como artrite reumatoide, vasculites de pequenos vasos associadas ao ANCA, à policondrite recidivante, ao lúpus eritematoso sistêmico e à doença de Crohn. O tratamento inclui o uso de corticoide em dose alta e em alguns casos o uso concomitante de imunossupressores, como metotrexate, azatioprina, micofenolato mofetil, ciclofosfamida ou ciclosporina. O uso de agentes imunobiológicos pode ser uma estratégia nos casos de

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difícil controle. Os autores descrevem o tratamento de três pacientes que após falha ao uso de corticoide ou imunossupressores apresentaram boa resposta após o uso de infliximabe.

Introduction

The peripheral cornea is situated very close to the conjunctiva, which has the critical elements for generating an immune response. As compared with the central cornea, this corneal region has a greater number of inflammatory cells, allowing the formation of immune complexes.[1]

Peripheral ulcerative keratitis is a destructive process that involves inflammation of the perilimbal cornea[1] and overlying epithelial defects.[2] The diseases commonly involved in this region are Mooren ulcers, autoimmunity against the cornea itself,[1] or manifestations of systemic disease,[3] especially rheumatoid arthritis and vasculitides.[4] When the peripheral corneal ulcer is accompanied by necrotizing scleritis, perforation and consequently loss of vision can occur, which confirms the severity of this eye disease.

The treatment of this disease includes corticosteroids in the acute phase and immunosuppressants in severe peripheral ulcerative keratitis, especially when associated with systemic disorders. Recently, the use of biological agents such as rituximab, an antibody against CD20, and monoclonal antibodies against pro-inflammatory cytokine TNF alpha (tumor necrosis factor) has been shown to be an alternative.[5–8]

Case reports

Case 1

Male patient, 20 years old, five years with recurrent red eye and eye pain. An ophthalmological investigation found the presence of peripheral ulcerative keratitis; the patient was introduced in topical steroids, prednisone 20 mg/day and NSAIDs, without improvement. The picture evolved with increased peripheral ulceration, significant conjunctival inflammatory component, and increased pain. Two years ago the patient received pulse therapy with methylprednisolone 1 g/day for three days, and infliximab was started at a dose of 3 mg/kg at weeks zero, two and six, and then every eight weeks, with significant improvement of ulceration, hyperemia, and eye pain. Currently, the patient remains in the use of only infliximab, without recurrence of ocular inflammation.

Case 2

Female patient, 59 years old, diagnosed with peripheral ulcerative keratitis for 10 years, but with symptoms of red eye and eye pain for 17 years. Treated with prednisone 40 mg/day and cyclosporin 3 mg/kg/day, with no response. During evolution, methotrexate was associated with the medication, and due to non-improvement, methotrexate was replaced by azathioprine. After a further failure of this new therapeutic combination (azathioprine and cyclosporine), three years ago infliximab was started at a dose of 3 mg/kg at intervals of eight weeks, with excellent response. Currently, the patient exhibits corneal injury healing, with no evidence of recurrence of perilesional inflammation.

Case 3

Male patient, 36 years old. Started seven years ago with recurrent episodes of severe eye pain, red eye and photophobia. An ulcer was diagnosed in perilimbar cornea, with frequent recurrence. The patient was treated with prednisone 60 mg and cyclosporine; without response. Due to clinical worsening of his eye disease and the difficulty in reducing the dose of corticosteroids, infliximab was started at a dose of 3 mg/kg at weeks zero, two and six and then every eight weeks, with almost complete resolution of the corneal lesion.

Discussion

Peripheral ulcerative keratitis is a condition characterized by inflammation of the peripheral cornea that causes ulceration of difficult resolution,[2] which can occur in isolation or as part of a systemic inflammation.[9,10] Multiple infections can determine corneal ulcer; thus, the differential diagnosis is critical.[10]

Approximately 50% of cases of non-infectious peripheral ulcerative keratitis are associated with some connective tissue disease,[5,11] especially rheumatoid arthritis. Other etiologies include polyarteritis nodosa, relapsing polychondritis, vasculitis associated with ANCA, for example, granulomatosis with polyangiitis (Wegener's) and granulomatosis with eosinophilic polyangiitis (Churg-Strauss syndrome).[5,9,12] A study published in 2012 showed that 211 of 701 patients with granulomatosis with polyangiitis had some ocular involvement in the diagnosis and 147 others developed the condition in the course of the disease. Among the changes found, peripheral ulcerative keratitis was observed.[13]

The corneal signals are similar in those various diseases causing the problem: red eye, pain, photophobia and corneal opacity.[5,9] This condition may occur after several years of systemic disease, or may be its first manifestation.[9,12]

Peripheral ulcerative keratitis is associated with high visual and systemic morbidity. Its complications are perforation of the cornea and decreased visual acuity. Inflammation of the eye may be an initial presentation of a systemic inflammatory disease with subclinical involvement of other organs and systems of the human body.[9]

The treatment for this condition is difficult and is based on the severity of corneal symptoms and on the extent of extraocular disease.[9] Initially, the treatment consists of topical and systemic corticosteroids, such as prednisone at 1 mg/kg/day; this treatment might not be able to promote remission.[3,4,7] The use of immunosuppressants may be tempted, in view of the

severity of the disease and the risk of vision loss.[14] Cyclophosphamide PO (2 mg/kg/day) or in monthly intravenous pulses may be used in conjunction with glucocorticoids in cases with risk of perforation or in the context of systemic vasculitides. Some patients may respond to the use of methotrexate, as demonstrated in a case report of a 25 year-old woman who had a significant improvement of idiopathic peripheral ulcerative keratitis with 10 mg of methotrexate per week and, after four weeks, the dose was increased to 25 mg, with excellent response.[15] Cyclosporine is an option to be attempted, with reports of response in cases of Mooren's ulcer.[16] Furthermore, the use of immunobiological products such as rituximab, a monoclonal antibody against CD20 expressed by lymphocytes B in granulomatosis with polyangiitis,[5] and especially infliximab, an anti-TNF, can produce a quick response in the suppression of corneal inflammation and of pain, thus determining the clinical improvement in cases of difficult control, such as in the patients here reported.[5,7,8,13,15,17] The cytokine TNF is important in the pathogenesis of peripheral ulcerative keratitis, both in idiopathic cases, as in those associated with rheumatoid arthritis or vasculitis. TNF stimulates the activity of metalloproteinases, in particular MMP-9, which has been confirmed in a dose-dependent manner in cultured human corneal epithelial cells. The increased expression and activity of MMP-9 were demonstrated in samples of human cornea with ulcerative keratitis. Thus, the inhibition of the cytokine TNF with the use of monoclonal antibodies can reduce the inflammation and destruction of extracellular matrix and corneal collagen degradation due to an unregulated activity of matrix metalloproteinases.[18–20]

Odorcic et al. in their study reported that there is not a recommended dose of infliximab in cases of peripheral ulcerative keratitis, and that reducing the interval between infusions to once every four weeks may be necessary.[4] Galor et al. showed, in a study, stability in visual acuity in 68% of 12 patients with rheumatoid arthritis associated with peripheral ulcerative keratitis, following treatment with cyclophosphamide or methotrexate.[9]

In the three cases here presented, we had favorable responses to infliximab in the treatment of ulcerative keratitis, prescribed after failure of corticosteroids and/or immunosuppressants, like other publications. Moreover, there was no recurrence of peripheral ulcerative keratitis in any of the three patients reported by us. All three cases showed no association with connective tissue diseases. Randomized, controlled trials with a larger number of cases will give more support for the use of biologic therapy, in particular anti-TNF, in patients with this condition.

Conflicts of interest

The authors declare no conflicts of interest.

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