

## *Infliximab in relapsing polychondritis*

Ana Paula Soares de Barros<sup>1</sup>, Nilton Akeshi Nakamura<sup>2</sup>, Thiara de Freitas Borges Santana<sup>3</sup>,  
Janaina Queiroz dos Santos Motta<sup>4</sup>, Washington Alves Bianchi<sup>5</sup>

### ABSTRACT

Relapsing Polychondritis (RP) is a rare systemic disease of unknown etiology, characterized by recurrent inflammation of cartilaginous structures and other connective tissues, including the ears, nose, joints, respiratory tract, and others. Due to the presence of typical signs and symptoms, biopsy is seldom necessary. Treatment includes corticosteroids, occasionally associated with immunosuppressive agents, but refractory cases are described. Recent reports suggest that anti-TNF agents, such as infliximab, may be of value in patients who do not respond to conventional therapy, but experience with this treatment is scarce. In this paper, the authors report the case of a patient with RP refractory to combined treatment with corticosteroids and immunosuppressive agents, who showed a good response to infliximab.

**Keywords:** relapsing polychondritis, therapy, infliximab.

### INTRODUCTION

Relapsing Polychondritis (RP) is a rare disorder of unknown etiology, characterized by recurring inflammation and destruction of cartilaginous structures, such as the ears, nose, larynx, and tracheobronchial tree.<sup>1</sup> Systemic manifestations could also involve the skin, eyes, blood vessels, and joints. It can affect individuals of any age group, but its incidence is higher around the 4<sup>th</sup> and 5<sup>th</sup> decades, without preference for race or gender, or family aggregation.

Its etiology remains unknown, but evidence suggests that autoimmune inflammation leads to the destruction of cartilages by proteolytic enzymes. The diagnosis is based on clinical criteria,<sup>2</sup> but biopsy confirmation is necessary in atypical cases. Zeuner *et al.* (1997) suggested the presence of a genetic factor associated with the human leukocyte antigen HLA-DR4.<sup>3</sup>

Uni or bilateral inflammation of the ear cartilage is the most frequent clinical manifestation. Different cartilages can be involved in successive bouts of the disease.<sup>2</sup>

Initially, auricular chondritis could be mistaken by an infectious etiology (leprosy or leishmaniasis) or trauma. In

the presence of respiratory tract involvement, pathologies like Wegener's granulomatosis, amyloidosis, sarcoidosis, osteochondroplastic tracheobronchopathy, and rhinoscleroma, which have similar presentation, should be ruled out. The differential diagnosis with Cogan's syndrome, Behçet's disease, Takayasu arteritis, Ehlers-Danlos syndrome, syphilis, cystic medial sclerosis, and spondyloarthropathies is mandatory in the presence of vascular lesions.<sup>4,5,6</sup>

The treatment of RP is empirical, adjusted according to the activity and severity of the disease<sup>7</sup>. In mild cases, the use of non-steroidal anti-inflammatories, colchicine, and dapsone are indicated.<sup>7,8</sup> Prednisolone is the main drug used in the treatment of this disorder. Immunosuppressors, such as methotrexate, cyclophosphamide, azathioprine, chlorambucil, mycophenolate mofetil, and cyclosporin, can be effective, but refractory cases can be seen.<sup>9,10</sup>

This report describes the clinical evolution of a patient who had a good response to infliximab after unsuccessful treatment with conventional therapy.

Received on 12/12/2008. Approved on 05/07/2009. We declare no conflict of interest.

39th Rheumatology Ward; Santa Casa da Misericórdia do Rio de Janeiro.

1. Physician, Post-Graduate Degree in Rheumatology from Santa Casa da Misericórdia do Rio de Janeiro

2. Physician, Post-Graduate Degree in Rheumatology from Santa Casa da Misericórdia do Rio de Janeiro

3. Physician, Post-Graduate Degree in Rheumatology from Santa Casa da Misericórdia do Rio de Janeiro

4. Assistant Physician of the Rheumatology Department of Santa Casa da Misericórdia do Rio de Janeiro

5. Chief of the Rheumatology Department of Santa Casa da Misericórdia do Rio de Janeiro

Correspondence to: Washington Alves Bianchi. Rua Santa Luzia, 206, Castelo – Rio de Janeiro – RJ. CEP: 20020-020. E-mail: wbianchi@yahoo.com.br

## CASE REPORT

**Identification:** E.V.F., 42 years old white female, married, from Nova Friburgo, Rio de Janeiro, seamstress.

**Clinical History:** The patient referred a 12-month history of pain in the sternal region, shoulders, temporomandibular joints, elbows, wrists, hands, knees, ankles, and feet; hoarseness, progressive hearing loss, dyspnea, left auricular chondritis, and vertigo. She was seen by a rheumatologist in her hometown, and received the diagnosis of relapsing polychondritis after auricular biopsy, which showed fragmented cartilaginous tissue surrounded by fibrous connective tissue, with mononuclear inflammatory infiltrate, suggestive of fibrosis, with areas of perichondral inflammatory reaction. Symptoms persisted despite treatment with prednisone, 40 mg/day, and methotrexate, 7.5 mg/week. Due to the poor response to treatment, the patient was referred to the Rheumatology Department of Santa Casa de Misericórdia do Rio de Janeiro. The dose of methotrexate was increased to 10 mg/week, the dose of prednisone remained the same, and calcium carbonate, folic acid, and clonazepam were added to the treatment. Laboratorial exams (Table 1) showed erythrocyte sedimentation rate (ESR) of 43 mm/h and C-reactive protein (CRP) of 6 mg/dL. Her symptoms worsened and she developed arthritis of ankles and wrists, diffuse body pain, and persistent left auricular chondritis and vertigo. Azathioprine, 100 mg/day, was added to the therapeutic regimen after the doses of methotrexate and prednisolone were increased to 15 mg/week and 60 mg/day, respectively. Her symptoms did not improve and the patient developed arthritis of the wrists and sternoclavicular joints, as well as right auricular pain. She complained of fever, epigastric pain, and odynophagia. Upper GI endoscopy showed *Candida*

esophagitis Kodsi I, mild endoscopic enanthematous pangastritis, gastric biopsy with mild erosive gastritis of the antrum and positive for *Helicobacter pylori*. The patient was treated with pantoprazole, amoxicillin, and metronidazole for 14 days, besides fluconazole. Laboratorial exams showed an increase in ESR to 92 mm/h and CRP+/4+. The dose of azathioprine was increased to 150 mg/day while maintaining the doses of the remaining drugs. Auricular chondritis improved after two months, with persistent polyarthritis of wrists, ankles, and sternoclavicular joints. Erythrocyte sedimentation rate remained elevated (76 mm/h). Her body aches were more severe and polyarthritis persisted. Due to treatment failure, infliximab was initiated: 3 mg/kg of infliximab in a patient weighing 63 kg (189 mg per infusion) on days 0, 14, and 42, followed by maintenance doses every eight weeks, as recommended for rheumatoid arthritis.

The patient referred improvement of the arthritis after the second infusion. After the third infusion, arthritis had remitted and objective inflammatory exams showed improvement (Chart 1). The patient referred progressive clinical improvement after each infusion, which allowed the reduction of the doses of corticosteroids and immunosuppressants to 10 mg/day of prednisolone and 7.5 mg/week of methotrexate.

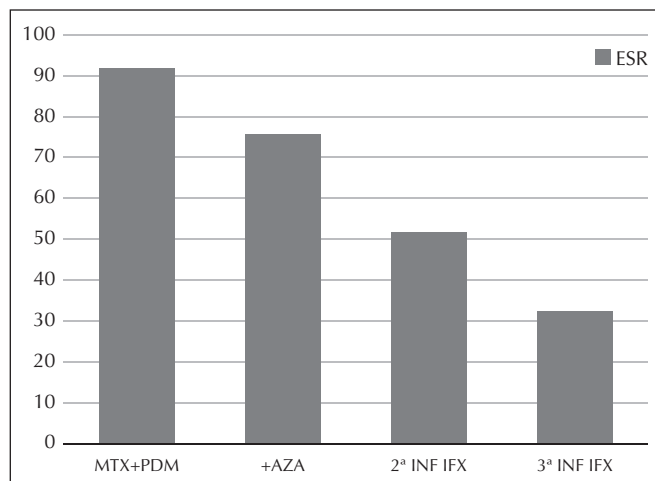
## DISCUSSION

The treatment for this patient was discussed throughout the follow-up, since a completely satisfactory treatment for RP does not exist. The literature has references on the use of pulse therapy with methylprednisolone and/or cyclophosphamide, as well as the use of immunosuppressants, such as methotrexate, azathioprine, and mycophenolate mofetil, with different

**Table 1**

Main Laboratorial Exams substitua a legenda por Laboratory results

Exam	Results	Exam	Results
Hemoglobin	12.3 g/dL	24-hour Proteinuria	69 mg/24h
Leukocytes	5,000 mm <sup>3</sup>	ANF HEp 2	Negative
Albumin	4.0 g/dL	Rheumatoid factor, latex and Waaler - Rose	Negative
Globulin	4.20 g/dL	ANCA	Negative
Platelets	288,000 mm <sup>3</sup>	Anti-DNA	Negative
ESR	43 mm/h	Anti-CCP	Negative
CRP	6 mg/dL	Anti-cardiolipin	Negative
AST	13 U/L	Lupus anticoagulant	Negative
ALT	19 U/L	Anti-HIV	Negative
UA	No changes	PPD	Weak reactor
VDRL	Negative	Serologies for hepatitis B and C	Negative

**Chart 1**

Variation of the erythrocyte sedimentation rate after starting the treatment

MTX: Methotrexate; PDM: Prednisolone + AZA – Azathioprine; INF IFX: Infliximab infusion.

results, in cases refractory to oral corticosteroids.<sup>11</sup> Besides, the successful treatment of refractory RP and cases with involvement of the respiratory tract with Tumor Necrosis Factor  $\alpha$  – TNF- $\alpha$  – antagonists have been reported.<sup>12</sup>

This patient was treated with infliximab, with initial dose of 3 mg/kg per infusion, as described. The experience obtained with our case suggests that infliximab can be useful in selected cases of RP unresponsive to the usual treatment.

Recent studies<sup>13,14</sup> have reported the use of this drug in patients undergoing surgical reconstruction of the nasal cartilage, as well as other biological agents like tocilizumab,<sup>15</sup> etanercept,<sup>16</sup> and adalimumab in patients who failed treatment with infliximab. Those reports confirm the need of more studies on the use of new drugs in the treatment of refractory cases of RP.

Since the patient had a weak response to PPD without confirmed history of tuberculosis, a CT scan of the chest was done, which did not show any changes. The case was also evaluated by the Pneumology Department and, after reaching a consensus on the use of biological agents, it was decided that prophylaxis with isoniazid was not necessary, but surveillance and proper follow-up were maintained.

Despite the benign evolution, the data in the literature recommend an observational attitude because the patient is at risk of future relapses with more severe disease manifestations. In this patient, we decided to use a drug that is not well-known or indicated for this pathology based on reports of successful treatment of RP and the absence of adverse events. Failure of the treatment used routinely to control the inflammatory activity was fundamental for the indication of biological therapy in an attempt, so far effective, to induce clinical

remission of the osteoarticular involvement and prevent further relapses that could cause further compromise and extend more severe RP to other organs and tissues.

## REFERÊNCIAS

### REFERENCES

- Harris jr ED, Budd RC, Firestein GS, Genovese MC, Sergent JS, Ruddy S *et al.* Kelley's textbook of rheumatology. 8 Ed. Pennsylvania: Elsevier; 2008.
- Mcadam LP, O'Hanlan MA, Bluestone R, Pearson CM. Relapsing polychondritis. Prospective study of 23 patients and review of the literature. *Medicine (Baltimore)* 1976; 55:193-215.
- Zeuner M, Straub RH, Rauh G, Albert ED, Scholmerich J, Lang B. Relapsing polichondritis: clinical and immunogenic analysis of 62 patients. *J Rheumatol* 1997; 24:96-101.
- Jeffrey B, Choi YW, Thomas H, Nancy A, McaAdams P. Relapsing polychondritis affecting the lower respiratory tract. *Am J Roentgenol* 2002; 178(1):173-7.
- Laura F, barton F. Uncommon ct findings in relapsing polychondritis. *Am J Neuroradiol* 2005; 26:2134-6.
- Karen L, Armin E, David T, William L, David K, Phillip B. Relapsing polychondritis: prevalence of expiratory ct airway abnormalities. *Radiology* 2006; 240(2):565-73.
- Trentham DE, Le CH. Relapsing polychondritis. *Ann Intern Med* 1998; 129(2):114-22.
- Francès C, el Rassi R, Laporte JL, Rybojad M, Papo T, Piete JC. Dermatologic manifestations of relapsing polychondritis. A study of 200 cases at a single center. *Medicine (Baltimore)* 2001; 80:173-9.
- Richez C, Dumoulin C, Coutouly X, Schaevebeke T. Successful treatment of relapsing polychondritis with infliximab. *Clin Exp Rheumatol* 2004; 22(5):629-31.
- Saadoun D, Deslandre CJ, Allanore Y, Pham XV, Kahan A. Sustained response to infliximab in 2 patients with refractory relapsing polychondritis. *J Rheumatol.* 2003; 30(6):1394-5.
- Rapini RP, Warner NB. Relapsing polychondritis. *Clin dermatol.* 2006; 24(6):482-5.
- Carter JD. Treatment of relapsing polychondritis with a tnf antagonist. *J Rheumatol.* 2005; 32(7):1413.
- Bell D, Wright D, Witt PD. Durability of nasal reconstruction in an adolescent with relapsing polychondritis treated with infliximab. *Plast Reconstr Surg* 2007; 120(4):1087-8.
- Ratzinger G, Kuen-Spiegl M, Sepp N. Successful treatment of recalcitrant relapsing polychondritis with monoclonal antibodies. *J Eur Acad Dermatol Venereol* 2009; 23(4):474-5.
- Kawai M, Hagihara K, Hirano T, Shima Y, Kuwahara Y, Arimitsu J *et al.* Sustained response to tocilizumab, anti-interleukin-6 receptor antibody, in two patients with refractory relapsing polychondritis. *Rheumatology (Oxford)* 2009; 48(3):318-9.
- Subrahmanyam P, Balakrishnan C, dasgupta b. Sustained response to etanercept after failing infliximab, in a patient with relapsing polychondritis with tracheomalacia. *Scand J Rheumatol* 2008; 37(3):239-40.
- Seymour MW, Home DM, Williams RO, Allard Sa. Prolonged response to anti-tumour necrosis factor treatment with adalimumab (humira) in relapsing polychondritis complicated by aortitis. *Rheumatology (oxford)* 2007; 46(11):1738-9.