



Sociedad Española  
de Reumatología -  
Colegio Mexicano  
de Reumatología

# Reumatología Clínica

www.reumatologiaclinica.org



## Case report

### Cat Scratch Disease During Etanercept Therapy in a Rheumatoid Arthritis Patient<sup>☆</sup>

Alberto O. Orden,<sup>a,\*</sup> Norma N. Nardi,<sup>b</sup> Alicia B. Vilaseca,<sup>c</sup> Ana C. Colombini,<sup>d</sup>  
Nora G. Barrios,<sup>e</sup> Anahí Vijnovich Barón<sup>f</sup>

<sup>a</sup> Servicio de Medicina Interna, Clínica San Camilo, Ciudad Autónoma de Buenos Aires, Argentina

<sup>b</sup> Servicio de Reumatología, Clínica San Camilo, Ciudad Autónoma de Buenos Aires, Argentina

<sup>c</sup> Servicio de Hematología, Clínica San Camilo, Ciudad Autónoma de Buenos Aires, Argentina

<sup>d</sup> Servicio de Infectología, Clínica San Camilo, Ciudad Autónoma de Buenos Aires, Argentina

<sup>e</sup> Servicio de Bacteriología, Clínica San Camilo, Ciudad Autónoma de Buenos Aires, Argentina

<sup>f</sup> Centro de Patología y Citología (CEPACIT), Ciudad Autónoma de Buenos Aires, Argentina



#### ARTICLE INFO

##### Article history:

Received 24 July 2016

Accepted 20 January 2017

Available online 21 July 2018

##### Keywords:

Cat scratch disease

*Bartonella*

Etanercept

Rheumatoid arthritis

#### ABSTRACT

Cat scratch disease (CSD) is an infectious disorder caused by *Bartonella henselae* and characterized by fever and granulomatous lymphadenopathy. Immunosuppression is a risk factor for the development of atypical forms of the disease. We report the case of a 52-year-old woman who presented with fever and bilateral inguinal lymph node enlargement. She did not have apparent contact with animals. The patient was receiving etanercept therapy for rheumatoid arthritis. Lymph node biopsy demonstrated granulomatous lymphadenitis. She was successfully managed by discontinuing etanercept and by treatment with minocycline. She developed clinical remission and typical seroconversion. Infection with *Bartonella* should be considered in the differential diagnosis in rheumatoid arthritis patients with lymphadenopathy of unknown origin.

© 2017 Elsevier España, S.L.U. and Sociedad Española de Reumatología y Colegio Mexicano de Reumatología. All rights reserved.

### Enfermedad por arañazo de gato en paciente con artritis reumatoidea tratado con etanercept

#### RESUMEN

La enfermedad por arañazo de gato (EAG) es una enfermedad infecciosa causada por la proteobacteria *Bartonella henselae*, caracterizada por fiebre y linfadenopatía granulomatosa. La inmunosupresión es un factor de riesgo para el desarrollo de formas atípicas de la enfermedad. Presentamos el caso de una mujer de 52 años de edad que presentó fiebre y adenomegalias inguinales bilaterales. No tenía contacto aparente con animales. La paciente estaba recibiendo tratamiento con etanercept por artritis reumatoidea. La biopsia del ganglio linfático informó de una adenopatía granulomatosa. Evolucionó favorablemente con la interrupción de etanercept y el tratamiento con minociclina. Presentó remisión clínica y la seroconversión típica. La infección por *Bartonella* debería ser considerada como un diagnóstico diferencial en pacientes con artritis reumatoidea, con linfadenopatía de origen desconocido.

© 2017 Elsevier España, S.L.U. y Sociedad Española de Reumatología y Colegio Mexicano de Reumatología. Todos los derechos reservados.

##### Palabras clave:

Enfermedad por arañazo de gato

*Bartonella*

Etanercept

Artritis reumatoidea

<sup>☆</sup> Please cite this article as: Orden AO, Nardi NN, Vilaseca AB, Colombini AC, Barrios NG, Vijnovich Barón A. Enfermedad por arañazo de gato en paciente con artritis reumatoidea tratado con etanercept. Reumatol Clin. 2018;14:303–306.

\* Corresponding author.

E-mail addresses: [aorden@intramed.net.ar](mailto:aorden@intramed.net.ar), [aorden@yahoo.com.ar](mailto:aorden@yahoo.com.ar) (A.O. Orden).

## Introduction

The proteobacterium *Bartonella henselae* (BH) is a small aerobic Gram-negative bacillus, that is highly adaptable to several mammals as reservoirs. In humans it produces cat-scratch disease (CSD), characterized by self-limiting fever and granulomatous lymphadenopathy. In 5%–15% of cases, it can lead to severe forms with ocular, glandular, neurological, pulmonary and/or osteoarticular involvement or thrombocytopenic purpura.<sup>1,2</sup>

The utilization of biological agents in individuals with rheumatic diseases, frequently in contact with household pets, increases concern about the development of opportunistic diseases, especially with atypical presentation.<sup>3–9</sup>

## Case Report

The patient was a 52-year-old woman with a 29-year history of rheumatoid arthritis (RA). She had received treatment with methotrexate, leflunomide and meprednisone (MP). At the age of 45 years, she was diagnosed with “diffuse sclerosing glomerulopathy and amyloidosis”. Thus, treatment was begun with etanercept at a dose of 50 mg/week, and her clinical signs improved.

Thirty days before visiting her physician, she developed a febrile syndrome and self-limiting diarrhea (one week). She had no apparent contact with animals. At admission, she was subfebrile, weak, adynamic, anorexic and had myalgia and arthralgia. Physical examination revealed bilateral painful inguinal lymphadenopathy, with no other relevant signs. An echocardiogram and respiratory function tests were normal. Chest and abdominal computed tomography demonstrated only inguinal lymph node enlargement.

Laboratory tests revealed hematocrit at 33%, hemoglobin: at 10.8 g/dL, white blood cells at 8500/mm<sup>3</sup> (neutrophils, 72%, lymphocytes, 19%, monocytes, 6%, eosinophils, 2% and basophils, 1%). Erythrocyte sedimentation rate: 110 mm/h; C-reactive protein: 10.2 mg/dL; glucose; 93 mg/dL; urea; 62 mg/dL; creatinine; 2.4 mg/dL; ferritin: 232 ng/mL (normal range: 12–150 ng/mL). The hepatic profile was normal,  $\beta_2$  microglobulin was 12.6 mg/dL (normal range: 0.8–2.2 mg/dL); immunoglobulin (Ig) A: 668 mg/dL; IgG: 1680 mg/dL and IgM: 174 mg/dL.

Tumor markers (cancer antigen [CA] 15-3, CA 19-9, CA-125 and carcinoembryonic antigen [CEA]) were negative. Virus serology (human immunodeficiency virus and hepatitis B and C viruses and syphilis (the Venereal Disease Research Laboratory test) were negative. There was no evidence of acute infection by cytomegalovirus, Epstein-Barr or toxoplasmosis. Blood and urine cultures were also negative.

The biopsy of a lymph node revealed a histological picture of “granulomatous lymphadenitis”, which suggested a diagnosis of CSD (Fig. 1). Periodic acid Schiff (PAS), Grocott and Ziehl-Neelsen stains were negative. Immunohistochemistry (cluster of differentiation [CD] 3, CD20) showed residual lymphocytes. Flow cytometry revealed no evidence of a lymphoproliferative process. Tests and cultures for common microorganisms, mycobacteria and fungi were negative. We did not detect *Chlamydia trachomatis*, atypical mycobacteria or *Mycobacterium tuberculosis* in the methods based on polymerase chain reaction.

Serological tests for BH showed that the patient was positive for IgM with a titer of 1:32 (cutoff value: 1:16) and for IgG with a titer of 1:160 (cutoff value: 1:10). With the diagnosis of CSD, treatment was begun with minocycline at a dose of 100 mg/12 h/12 weeks, which achieved the remission of the symptoms and of lymphadenopathy. Once treatment had been completed, IgM was negative and the IgG titer had increased to 1:320. Treatment with etanercept was reinitiated to control RA, without unforeseen eventualities.

## Discussion

Cat-scratch disease especially affects children and young adults, only rarely involving elderly individuals, and is associated with contact with animals (which did not occur in our patient). We report, to the best of our knowledge, the first case of CSD in a patient with RA being treated with etanercept.

The diagnosis of CSD is based on a combination of clinical, epidemiological (contact), bacteriological, serological and histological findings. There is no diagnostic criteria considered as a reference pattern.<sup>10,11</sup>

In the immunocompetent host, it usually presents as subacute lymphadenopathy accompanied by fever and mild involvement of general health, although there can be atypical manifestations such as fever of unknown origin, hepatosplenic granulomas, neuroretinitis, seizures, osteomyelitis, etc.<sup>1,2,10,11</sup>

In immunocompromised patients, there are reports of bacteremia, endocarditis, bacillary angiomatosis and peliosis hepatis.<sup>1–11</sup> Our patient presented with a prolonged febrile syndrome and inguinal lymphadenopathy.

The primary lesion developed near the site of inoculation, 3–10 days after the scratch or bite. The immune response includes an increase in the response of T helper cells mediated by interferon- $\gamma$  and macrophage recruitment and stimulation, with the formation of granulomas. During infection, the infected macrophages produce high levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Thus the use of TNF- $\alpha$  inhibitors interferes with the inflammatory response, favoring the dissemination and bacteremia of BH.<sup>2,11</sup>

The lack of exposure to cats can be explained by the fact that other animals (arthropods) can transmit the bacteria. It is known that many patients with CSD deny having had any contact with cats.<sup>12,13</sup>

A review of the literature on CSD in patients who received biological agents (Table 1) demonstrated that lymphadenopathy is reported in all the articles, but only in three of eight patients was the lesion or entry site identified. Fever, present in the patients taking etanercept, did not occur in every case.<sup>3–9</sup>

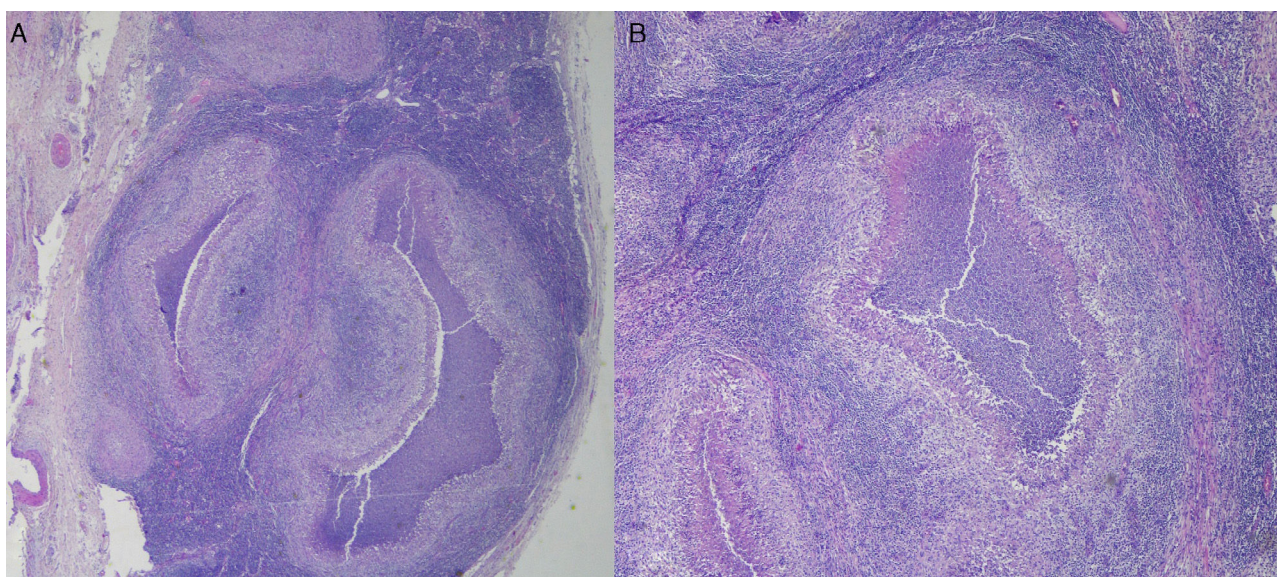
The microbiological diagnosis of BH is mostly based on the detection of antibodies by indirect immunofluorescence (IIF) or enzyme-linked immunosorbent assay (ELISA). The IgG titers in the general population vary with the risk of exposure. A titer of IgG  $\geq$ 1:64 is considered to be indicative of the diagnosis (sensitivity and specificity >90%). The duration of IgM is limited (3 months).<sup>14</sup>

Isolation in culture is very difficult (it requires 2–6 weeks) and, in general, is negative. This must be taken into account, especially in cases of fever of unknown origin, neuroretinitis, encephalitis, peliosis or bacillary angiomatosis and in endocarditis with negative cultures. Molecular tests in blood or tissues can be valuable.<sup>1,10–14</sup>

Histopathology, which is helpful for the differential diagnosis, serves as a guide but is not pathognomonic, and reveals necrotizing granulomas, microabscesses and follicular hyperplasia. Warthin–Starry stain only demonstrates the presence of bacilli in lymph nodes that contain suppurative granulomas. Thus, although negative, it does not rule out the diagnosis.<sup>15</sup> The differential diagnosis of granulomatous lymphadenitis includes an extensive spectrum of infectious causes (bacterial agents—among them BH, *chlamydias*, fungi, mycobacteria, parasites, spirochetes and *rickettsias*) and noninfectious causes (lymphatic or secondary neoplasms, vasculitis, Crohn’s disease, celiac disease, sarcoidosis, Kikuchi–Fujimoto disease, berylliosis, etc.).<sup>16</sup>

Treatment should primarily take into consideration the clinical manifestations and the immunological status of the patient. The recommendations are based on case reports and expert opinion, since there are few clinical trials.<sup>2,11,17,18</sup>

In immunocompetent individuals, the disease is generally self-limiting and may not require antibiotics. In a clinical trial with



**Figure 1.** Biopsy: (A) Lymph node displaced by large granulomas with a stellar form (hematoxylin–eosin, 2×). (B) Micro-abscessed with pyocytes, surrounded by a palisade of histiocytes encircled by small lymphocytes (hematoxylin–eosin, 4×).

**Table 1**  
Characteristics of Our Patient and Comparison With Cases Retrieved From the Literature Review.

Case report										
Sex	Age (y)	Disease	Drug	Source	Lymphadenopathy	Fever	Diagnosis	Treatment		
W	52	RA	Etanercept	?	Inguinal	Yes	IgM+, IgG+, Path	Minocycline		
Literature review										
Sex	Age (y)	Disease	Drug	Source	Lymphadenopathy	Fever	Diagnosis	Treatment		Ref.
M	51	PsA	Etanercept	L	Mesenteric, Splenic abscesses. Panniculitis	Yes	IgG+	Clarithromycin		3
M	50	AS	Etanercept	L	Cervical, submaxillary	Yes	IgG+, Path: PCR+	Doxycycline/Roxithromycin		4
W	74	Crohn's	Infliximab	C	Mesenteric, periceliac, mediastinal Panniculitis	Yes	IgG+	Tigecycline		5
W	23	AS	Infliximab	L	Inguinal. Subcutaneous nodes in arm	No	Path: W–S+	Moxifloxacin	Amikacin	6
M	36	RA	Tocilizumab	C	Axillary and mediastinal Subcutaneous nodes in arm	No	IgG+, Path: PCR+	Doxycycline	Gentamicin	7
M	29	sero–RA	Tocilizumab	C	Epitrochlear and axillary	No	IgG+, Path: W–S+	Azithromycin		8
M	36	Ps	Adalimumab	C	Cervical	No	AP: PCR+	Doxycycline		9

AS, ankylosing spondylitis; C, contact; L, lesion; M, man; Path, pathology; PCR, polymerase chain reaction; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; Ref., reference; sero–RA, seronegative rheumatoid arthritis; W, woman; W–S, Warthin–Starry stain; ?, unknown.

azithromycin, the use of the drug had a slight effect on the reduction of lymph node volume in a shorter period of time.

In the case of intolerance, other possibilities are clarithromycin, rifampicin, trimethoprim-sulfamethoxazole and ciprofloxacin. In immunocompromised patients and in atypical presentations, antibiotic therapy is always suggested. The recommended combinations in hepatosplenic or disseminated disease include rifampicin plus azithromycin or gentamicin and, in neurological disease or neuroretinitis, the use of doxycycline plus rifampicin is proposed.<sup>2,11,17,18</sup>

In patients taking biological agents the drugs most widely employed were tetracyclines and macrolides. The course in every case was favorable, with variable periods of remission, that were not immediate in the majority, but there were no relapses. Biological therapies could be reinitiated. as in our case, once the disease was under control.<sup>3–9</sup>

In short, we present the case of a woman with RA who was being treated with etanercept, with a clinical, serological and pathological diagnosis of CSD. Her response was favorable to the therapeutic approach. The increase in the use of biological agents and the number of families with pets should call attention to this condition, even in the absence of an evident lesion or contact with animals.

## Ethical Disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

## Conflicts of Interest

The authors declare they have no conflicts of interest.

## References

- Mazur-Melewska K, Mania A, Kemnitz P, Figlerowicz M, Służewski W. Cat-scratch disease: a wide spectrum of clinical pictures. *Postepy Dermatol Alergol.* 2015;32:216–20.

2. Rolain JM, Brouqui P, Koehler JE, Maguina C, Dolan MJ, Raoult D. Recommendations for treatment of human infections caused by *Bartonella* species. *Antimicrob Agents Chemother.* 2004;48:1921–33.
3. Schiffmann A, Pers YM, Lukas C, Combe B, Morel J. Mesenteric and splenic cat-scratch disease during etanercept therapy. *Rheumatology (Oxford).* 2009;48:1461–2.
4. Mathieu S, Vellin JF, Poujol D, Ristori JM, Soubrier M. Cat scratch disease during etanercept therapy. *Joint Bone Spine.* 2007;74:184–6.
5. Cañas-Ventura A, Esteve E, Horcajada JP, Andreu M, Knobel H, Márquez L. Systemic *Bartonella henselae* infection and Crohn's disease treatment with infliximab. *Inflamm Bowel Dis.* 2012;18:E197–8.
6. Zhou Y, Yin G, Tan C, Liu Y. Cat scratch disease during infliximab therapy: a case report and literature review. *Rheumatol Int.* 2015;35:911–3.
7. Milin M, Acquitter M, Le Berre R, Sassolas B, Devauchelle-Pensec V, Cornec D. *Bartonella henselae* infection during tocilizumab therapy. *Joint Bone Spine.* 2013;80:221.
8. Singh N, Sinclair LL, Ijdo J. Cat-scratch fever and lymphadenopathy in a rheumatoid arthritis patient on tocilizumab. *J Clin Rheumatol.* 2015;21:40.
9. Osório F, Pedrosa A, Azevedo F, Figueiredo P, Magina S. Cat-scratch disease during anti-tumor necrosis factor-alpha therapy: case report and review of the literature. *Int J Dermatol.* 2014;53:e182–3.
10. American Academy of Pediatrics. Cat scratch disease (*Bartonella henselae*). In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, editors. *Red Book: 2012 Report of the Committee on Infectious Diseases.* Elk Grove Village, IL: American Academy of Pediatrics; 2012. p. 269–71.
11. Margileth AM. Recent advances in diagnosis and treatment of cat scratch disease. *Curr Infect Dis Rep.* 2000;2:141–6.
12. Breitschwerdt EB. Bartonellosis: one health perspectives for an emerging infectious disease. *ILAR J.* 2014;55:46–58.
13. Florin TA, Zaoutis TE, Zaoutis LB. Beyond cat scratch disease: widening spectrum of *Bartonella henselae* infection. *Pediatrics.* 2008;121:e1413–25.
14. Bergmans AM, Peeters MF, Schellekens JF, Vos MC, Sabbe LJ, Ossewaarde JM, et al. Pitfalls and fallacies of cat scratch disease serology: evaluation of *Bartonella henselae*-based indirect fluorescence assay and enzyme-linked immunoassay. *J Clin Microbiol.* 1997;35:1931–7.
15. Blanco JR, Raoult D. Diseases produced by *Bartonella*. *Enferm Microbiol Clin.* 2005;23:313–9.
16. Asano S. Granulomatous lymphadenitis. *J Clin Exp Hematop.* 2012;52:1–16.
17. Bass JW, Freitas BC, Freitas AD, Sisler CL, Chan DS, Vincent JM, et al. Prospective randomized double blind placebo-controlled evaluation of azithromycin for treatment of cat-scratch disease. *Pediatr Infect Dis J.* 1998;17:447–52.
18. Prutsky G, Domecq JP, Mori L, Bebko S, Matzumura M, Sabouni A, et al. Treatment outcomes of human bartonellosis: a systematic review and meta-analysis. *Int J Infect Dis.* 2013;7:e811–9.