Reumatol Clin. 2011;7(6):401–403

Reumatología Clínica

www.reumatologiaclinica.org

Case Report

Meningeal and Guillain–Barrè Syndrome in a Patient With Rheumatoid Arthritis Receiving Adalimumab Therapy☆

Pino López Méndez,[a,*] Idaira Martín Santana,[a] María del Pino Reyes Yánez,[a] Arminda Ruano Hernández,[a] José Ángel Hernández Beriain,[b] Miguel Hervás García[a]

[a] *Servicio de Neurología, Hospital Universitario Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain*
[b] *Servicio de Reumatología, Hospital Universitario Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain*

ARTICLE INFO

Article history:
Received 18 October 2010
Accepted 27 January 2011
Available online 25 November 2011

Keywords:
Tumor necrosis factor-alpha
Monoclonal antibodies
Rheumatoid arthritis
Meningeal syndrome
Guillain–Barrè syndrome

ABSTRACT

Adalimumab is a recombinant human monoclonal antibody that blocks the effects of tumor necrosis factor-alpha, and is presently used for treatment of rheumatoid arthritis, with demyelination being a potential adverse effect. A 31-year-old male with seropositive rheumatoid arthritis presented with diarrhea after the second injection of adalimumab. He was treated with ciprofloxacin. In a few days he developed a Guillain–Barrè syndrome confirmed by electromyography, and his cerebrospinal fluid was compatible with meningeal syndrome or partially treated bacterial meningitis. Adalimumab may be associated with the development of demyelination and infectious diseases. Moreover, both the central nervous system and the peripheral nervous system can be affected.

Síndrome meníngeo y síndrome de Guillain-Barrè en un paciente con artritis reumatoide tratado con adalimumab

Palabras clave:
Factor de necrosis tumoral alfa
Anticuerpos monoclonales
Artritis reumatoide
Síndrome meníngeo
Síndrome de Guillain-Barrè

RESUMEN

Adalimumab es un anticuerpo monoclonal recombinante humano que bloquea el efecto del factor de necrosis tumoral alfa. Actualmente se emplea como tratamiento para la artritis reumatoide, siendo la desmielinización un potencial efecto adverso. Nuestro caso trata de un varón de 31 años con artritis reumatoide seropositiva que presentó un cuadro diarreico después de la segunda dosis de adalimumab. Tras tratamiento con ciprofloxacino el paciente desarrolló un síndrome de Guillain-Barrè confirmado por electromiografía. El estudio del líquido cefalorraquídeo sugirió un síndrome meníngeo o una posible meningitis bacteriana decapitada. El tratamiento con adalimumab puede asociarse con el desarrollo de enfermedades desmielinizantes e infecciosas y afectar simultáneamente al sistema nervioso central y al periférico.

Introduction

Adalimumab is a recombinant human monoclonal antibody directed against tumor necrosis factor alpha (TNF-α) which significantly improves symptoms, limits joint damage progression, and leads to disability in patients with rheumatoid arthritis (RA).[1]

Among the known secondary effects related with adalimumab, skin reactions, reactivation of tuberculosis, congestive heart failure, lupus like syndromes, cytopenias, and worsening or onset of demyelinating neurologic diseases are found,[2] as well as rhinitis, headache, upper respiratory tract infections,[3] joint pain, nausea, diarrhea, and other more serious infections needing hospitalization and tumors.[4] Neurologic diseases associated to this treatment are Guillain–Barrè (SGB)[5–7] syndrome, Miller–Fisher

☆ Please cite this article as: López Méndez P, et al. Síndrome meníngeo y síndrome de Guillain-Barrè en un paciente con artritis reumatoide tratado con adalimumab. Reumatol Clin. 2011;7(6):401–3.

* Corresponding author.
E-mail address: plm_mf@hotmail.com (P. López Méndez).

2173-5743/$ – see front matter

(SMF)[6] syndrome, optic neuritis,[8] hypertrophic pachimeningitis,[9] meningitis due to *Lysteria monocytogenes*[10] and demyelinating encephalomyelitis.[11] However, infections have also been described which may constitute the causal agent of the process due to molecular mimicry induced immune mediated damage, and the resulting neurologic affection, as in the case of *Mycoplasma pneumoniae*.[12]

Clinical Case

We present the case of a 31-year-old male diagnosed with seropositive RA 5 years prior and had a negative Mantoux test. He was treated with sulphasalazine and leflunomide. Treatment was optimized with methotrexate 25 mg/week, deflazacort 12.5 mg/day and, because of the poor response, adalimumab was added at a dose of 40 mg every 2 weeks. After the second dose of adalimumab, the patient presented vomiting, diarrhea and fever, and was diagnosed as having acute gastroenteritis. After 72 h without improvement, treatment with ciprofloxacin was initiated. The patient then presented lower back pain, a reduction in muscle strength of the lower limbs 4/5 distal and 4+/5 proximal, arheflexia, difficulty for standing and walking and pain on cervical movement with neck rigidity and no other meningeal signs.

Lumbar puncture obtained 850 leukocytes/mm^3 (91% neutrophils), glucose 39 mg/dl (glucose: 144 mg/dl), proteins 155 mg/dl, no microorganisms on Gram stain and no acid-fast bacilli on Ziehl–Nielsen stain. Laboratory studies showed an ESR of 51 mm, a CRP 5.2 mg/l. The serologic study included HSV 1 and 2, VZV, CMV, EBV, HBV, HCV, HIV, *Coxiella burnetti*, *M. pneumoniae*, Parvovirus B19, *Salmonella*, *Shigella*, Proteus OX19, *Borrelia burgdorferi*, *Brucella abortus*, *Rickettsia typhi* and *R. conorii*, *Treponema pallidum*, and all of them resulted in negative. Anti-ganglioside GQ1b antibodies were not studied. No pathologic findings were seen on cranial, cervical, dorsal, and lumbar magnetic resonance. An electromyogram manifested a mixed sensitive-motor demyelinating polyneuropathy with affection of upper and lower limbs and signs of acute denervation, with a loss in axonal volume of the common left perineal nerves, which showed no latency, and both posterior tibialis nerves, with latencies of 5.15 ms on the left side and 6.55 ms on the right. The F wave of the left tibialis nerve was slightly lengthened (56.25 ms).

In the diagnosis of meningeal syndrome (possibly bacterial meningitis due to an unknown germ versus decapitated) and GBS, adalimumab was suspended and intravenous treatment with ceftriaxone, vancomycin, and ampicillin for the suspected meningitis, and immunoglobulin and hidrocortisone for GBS resulted with a good clinical progression.

Discussion

When administering a TNF-α antagonist, the drug may reach the nervous system through the roots and nerve terminals, where the blood brain barrier is insufficient or absent, and neutralizes it in the peripheral nervous system. Low levels of TNF-α may increase or prolong specific T cell responses to myelin and increase the risk of development of an immune mediated neuropathy by altering the intrinsic balance of TNF-α and its receptors in the peripheral nervous system.[13]

We present the case of a patient with a meningeal syndrome, probably related to bacterial meningitis due to an unknown germ, and GBS diagnosed based on clinical progression and the patients history. Other diagnoses, such as vasculitic neuropathy, diffuse polyneuropathy or germ-associated polyradiculoneuritis were ruled out by the symmetrical clinical presentation, electromyographic results and negative serology.

We propose three possibilities as an explanation for our case. First, cell induced immunosuppression due to adalimumab may facilitate both infectious processes (gastrointestinal infection and the resulting GBS, and the possible infectious meningitis). Second, both the diarrhea and the GBS may be adverse events from adalimumab, and the possible meningitis due to immunosuppression, decapitated due to antibiotics administered for diarrhea. Third, an infectious agent may be the cause of all of the symptoms due to immune mediated, induced damage due to molecular mimicry. Even then, we assume that this clinical picture is caused by the treatment with adalimumab due to the temporal association between the injection of the drug and the onset of symptoms.

There are case reports of patients with RA who develop demyelinating diseases such as MFS,[6] optic neuritis,[8,14] demyelinating encephalomyelitis[11] or mononeuritis multiplex[15] ranging in time from 1 month to 1 year after the onset of treatment with adalimumab, or GBS[5] and chronic inflammatory demyelinating polyneuropathy[16] between 2 weeks and 1 year after treatment onset with etanercept or infliximab, but none of them have shown two simultaneous manifestations.

Our patient could be the first case of demyelination of the peripheral nervous system described and infection of the central nervous system simultaneously. However, it is impossible to know if these clinical events are due to an associated opportunistic infection associated to cellular immunosuppression induced by adalimumab or a drug associated adverse event.

Acknowledgement

We wish to thank Dr. Jesús María Rodríguez Navarro for his guidance in the elaboration of this article.

References

1. Bomardieri S, Ruiz AA, Fardellone P, Geusens P, McKeena F, Unnebrink K, et al. Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. Rheumatology. 2007;46:1191–9.
2. Scheinfeld N. Adalimumab: a review of side effects. Expert Opin Drug Saf. 2005;4:637–41 [abstract].
3. Navarro-Sarabia F, Ariza-Ariza R, Hernández-Cruz B, Villanueva I. Adalimumab para el tratamiento de la artritis reumatoide, La Biblioteca Cochrane Plus. Oxford: Update Software Ltd.; 2008 Número 4. Available from: http://www.update-software.com [Translated from The Cochrane Library, 2008 Issue 3. Chichester, United Kingdom: John Wiley & Sons, Ltd.].
4. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy. A randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004;50:1400–11.
5. Shin IS, Baer AN, Kwon HJ, Papadopoulos EJ, Siegel JN. Guillain–Barré and Miller Fisher syndromes occurring with tumor necrosis factor α antagonist therapy. Arthritis Rheum. 2006;54:1429–34.
6. Kurmann PT, van Lindthoudt D, Kai-Lik So A. Miller–Fisher syndrome in a patient with rheumatoid arthritis treated with adalimumab. Clin Rheumatol. 2009;28:93–4.
7. Silburn S, McIvor E, McEntegart A, Wilson H. Guillain–Barré syndrome in a patient receiving anti-tumour necrosis factor α for rheumatoid arthritis: a case report and discussion of literature. Ann Rheum Dis. 2008;67:575–6.
8. Simsek I, Erdem H, Pay S, Sobaci G, Dinc A. Optic neuritis occurring with anti-tumour necrosis factor α therapy. Ann Rheum Dis. 2007;66:1255–8.
9. Ahmed M, Luggen M, Herman JH, Weiss KL, Decourten-Myers G, Quinlan JG, et al. Hypertrophic pachymeningitis in rheumatoid arthritis after adalimumab administration. J Rheumatol. 2006;33:2344–6.
10. Gil C, Legido J, Cuenca C, Santamaría A, Sacristán MV, Salvatierra C, et al. Meningitis due to *Listeria monocytogenes* during adalimumab therapy. Gastroenterol Hepatol. 2009;32:587–8.

11. Sillero Sánchez M, García Domínguez G, Asencio Marchante JJ. Demyelinating encephalomyelitis associated with treatment with adalimumab. Neurologia. 2010;25:136–8.
12. Tsiodras S, Kelesidis I, Kelesidis T, Stamboulis E, Giamarellou H. Central nervous system manifestations of *Mycoplasma pneumoniae* infections. J Infect. 2005;51:343–54.
13. Stübgen JP. Tumor necrosis factor-α antagonists and neuropathy. Muscle Nerve. 2008;37:281–92.
14. Chung JH, Van Stavern GP, Frohman LP, Turbin RE. Adalimumab-associated optic neuritis. J Neurol Sci. 2006;244:133–6.
15. Makol A, Grover M. Adalimumab induced mononeuritis multiplex in a patient with refractory rheumatoid arthritis: a case report. Cases J. 2008;1:287–8.
16. Alshekhlee A, Basiri K, Miles JD, Ahmad SA, Katirji B. Chronic inflammatory demyelinating polyneuropathy associated with necrosis factor-alpha antagonists. Muscle Nerve. 2010;41:723–7.