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Cryptococcal Meningoencephalitis in a Patient With Rheumatoid Arthritis Treated With Methotrexate and Prednisone*



Meningoencefalitis criptocócica en una paciente con artritis reumatoide tratada con metotrexato y prednisona

To the Editor:

Cryptococcus neoformans is an encapsulated biotrophic fungus that is transmitted as an aerosol.¹ Its origin has been identified in *Eucalyptus camaldulensis*, its infective forms are basidiospores and encapsulated yeast, and its vector is dried bird droppings, especially from pigeons.¹ Cryptococcal infections were commonly found in immunocompromised persons with alterations in cellular immunity.² Since the introduction of highly active antiretroviral therapy (HAART), the incidence of these infections has decreased dramatically due to better virological and immunological control, due to the decrease in viral load and increase in CD42 cell count. Cryptococcal infections have been reported in patients with a

history of prolonged use of corticosteroids, diabetes, renal disease, immunosuppressive therapy, solid organ transplant, lymphoma, sarcoidosis and idiopathic lymphopenia CD42. The cases of cryptococcal infection in patients with rheumatoid arthritis (RA) are limited to a few papers, and when reviewing the literature there are only 3 reported cases of cryptococcal meningitis as the admission diagnosis. We report the case of a young patient with RA, who was not undergoing biological therapy and presented a meningoencephalic syndrome. The patient is a 49-year-old woman with a history of RA for the past 5 years, treated with methotrexate 15 mg weekly and prednisone 15 mg/day; she came to the emergency department due to having suffered 4 days of intense occipital headache, progressive, incoherent speech, disorientation, with memory problems, drowsiness, and in the last 24 h, fever. Upon neurological examination she was markedly confused, with impaired memory, judgment and altered calculus and ocular tenderness. Laboratory tests showed: ESR: 63 mm/h; CRP 8.3 mg/dl; glucose 353 mg/dl, sodium 134 mg/dl. It was initially considered as a meningoencephalic syndrome. Lumbar puncture was performed, with an opening pressure of 31 cm H₂O, low glucose

Table 1
Cryptococcal Infections Reported in Patients With Rheumatoid Arthritis.

Age/Gender	Site of infection	Treatment	Comorbidity/Outcome	Reference
65/M	Pulmonary	MTX, HXQ, Infl	No/recovery	Shrestha et al. (2004)
44/M	Pulmonary	Pred, MTX, Lefl, Infl	No/recovery	Starrett et al. (2002)
69/M	Pulmonary	Pred, MTX, Infl	DM2/recovery	True et al. (2002)
47/F	Pulmonary	Pred, Infl	No/recovery	Arend et al. (2004)
61/M	Pulmonary	Pred, MTX, Lefl, Infl	No/recovery	Hage et al. (2003)
67/F	Meninges	Pred, MTX, Infl	No/recovery	Muñoz et al. (2007)
82/F	Pulmonary/meninges	Pred	?/Death	Tajiri et al. (2009)
80/M	Leather/disseminated	MTX, Pred	ERC/death	Diaz et al. (2010)
74/M	Skin	Pred	DM2/recovery	Moosbrugger et al. (2008)
58/F	Skin	MTX, HXQ, Adal	Trauma	Morgan et al. (2008)
49/F	Brain-meninges	MTX, Pred	DM2 de novo/treatment	Threshing et al. (2012)
70/M	Brain-meninges	Infl, Ritux, Pred, MTX	None	Wingfield et al. (2011)
Average age: 63.8	Pulmonary: 50%	MTX: 75%; Pred: Infl 75%; 50%; Lefl: HXQ 16%; 16%;	DM2: 16%; ERC: 8.3%	Percentage of patients according to variables
	Skin: 16%	Adal: Biological 8.3%; 66%		
	Meninges: 16%			
	Disseminated: 8.3%			

Adal: adalimumab; DM2: type 2 diabetes mellitus; F: female; HXQ: hydroxychloroquine; Infl: infliximab; Lefl: leflunomide; M: male; MTX: methotrexate; Pred: prednisolone; Ritux: rituximab.

Source: based on Muñoz et al. (2007).⁷

* Please cite this article as: Trillos RF, Fernández-Ávila DG, Díaz MC, Gutiérrez JM. Meningoencefalitis criptocócica en una paciente con artritis reumatoide tratada con metotrexato y prednisona. *Reumatol Clin.* 2014;10:346-347.

20 mg/dl, protein of 111 mg/dl, WBC 14 mm³, neutrophils 16%, lymphocytes 84 found %, gram stain + + + yeast and bacterial antigens, with encapsulated blastoconidias found after staining with China ink, compatible with *Cryptococcus* sp. Methotrexate and prednisone were discontinued or decreased. We started treatment with amphotericin B, in increasing doses up to 1 g intravenously, with an adequate clinical response and infection control. Due to the presence of *de novo* diabetes mellitus, treatment with insulin was started based on a recommendation of endocrinology.

Opportunistic CNS infections reported in patients with RA include progressive multifocal encephalopathy, aspergilloma, tuberculosis, infection with West Nile virus, bacterial meningitis, infection with rodococcus and cryptococcal meningitis; however, the patients who have been reported with these types of infection were undergoing biological therapy.^{3–5} Cryptococcal infections reported in RA patients are summarized in Table 1.^{6,8,9} When evaluating Table 1, it can be seen that most cryptococcal infections in patients with RA present in the lungs,¹⁰ followed by skin and meninges; one case showed spreading with multiorgan involvement and deadly consequences. The average age of presentation for any cryptococcal infection is 63.8 years (range: 47–82 years); the most frequently associated drugs are methotrexate and prednisone in 75% of cases. 66% of the patients who developed infections due to this micro-organism were on biological therapy. Of the 3 patients who presented cryptococcal meningitis, only the patient reported in this case was not undergoing biological therapy.

In conclusion, we report a case of cryptococcal meningitis in a patient with RA in non-biological antirheumatic treatment (glucocorticoids and methotrexate).

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Prosthesis Infection by *Mycobacterium tuberculosis* in a Patient With Rheumatoid Arthritis: A Case Report and Literature Review[☆]



Infección protésica por *Mycobacterium tuberculosis* en paciente con artritis reumatoide: reporte de un caso y revisión bibliográfica

To the editor:

Prosthetic knee infection by *Mycobacterium tuberculosis* (MT) is rare.^{1,2} Reviews in 2011 and 2013 found 7 and 15 cases of prosthetic infections due to MT, respectively.^{3–5} Since the introduction of biological treatment for rheumatoid arthritis (RA), there has been an increase in the incidence of infection by MT, mainly in patients treated with antagonists to tumor necrosis factor (anti-TNF).^{6,7} One study showed an MT infection rate of 49 per 100,000 person-years in patients with RA treated with anti-TNF versus 8.7^{6,7} in patients with RA not treated with these agents. Here, we present a case

of prosthetic infection by MT in a patient with RA treated with anti-TNF.

The patient is a 77-year-old woman who had RA treated with methotrexate 7.5 mg/weekly and infliximab (IFX) 3 mg/kg, and a right knee prosthesis. In March 2012 she developed cough, and fever with nightly sweating lasting for 2 months; BK and sputum culture were requested, both negative. She received IFX in May and in June went to a review visit referring multiple respiratory infections during that time. In August she was assessed by Orthopedics, finding fever, pain and swelling of the right knee; discharged with a suspected prosthetic infection (Fig. 1A). In November, she was hospitalized in Internal Medicine (IM) for partial bowel obstruction and was discharged on prednisone 15 mg/day; during admission, a computed tomography (Fig. 1B) was performed, showing a pulmonary nodule indicative of granuloma and chest and retroperitoneal lymphadenopathy. In January 2013 she came to the Rheumatology clinic due to knee pain, and IFX was suspended; she also was assessed by IM, who recommended surgery for the persistent intestinal subocclusion. In April, she was evaluated by General Surgery and operated. Pathologic examination showed necrotizing granulomatous lymphadenitis and necrotizing granulomatous inflammation and ulceration of the mucosa in the small intestine; microbiological study was negative for *Mycobacterium*. Rifater[®] was begun and QuantiFERON[®] performed, which

[☆] Please cite this article as: Egües Dubuc C, Uriarte Ecenarro M, Errazquin Aguirre N, Belzunegui Otano J. Infección protésica por *Mycobacterium tuberculosis* en paciente con artritis reumatoide: reporte de un caso y revisión bibliográfica. *Reumatol Clin*. 2014;10:347–349.