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

Meningoencephalitis cryptocócica 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. 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. Cryptococcal infections were commonly found in immunocompromised persons with alterations in cellular immunity. 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>
<thead>
<tr>
<th>Age/Gender</th>
<th>Site of infection</th>
<th>Treatment</th>
<th>Comorbidity/Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>65/M</td>
<td>Pulmonary</td>
<td>MTX, HXQ, Infl</td>
<td>No/recovery</td>
<td>Shrestha et al. (2004)</td>
</tr>
<tr>
<td>44/M</td>
<td>Pulmonary</td>
<td>Pred, MTX, Lefl, Infl</td>
<td>No/recovery</td>
<td>Starrett et al. (2002)</td>
</tr>
<tr>
<td>69/M</td>
<td>Pulmonary</td>
<td>Pred, MTX, Infl</td>
<td>No/recovery</td>
<td>True et al. (2002)</td>
</tr>
<tr>
<td>47/F</td>
<td>Pulmonary</td>
<td>Pred, Infl</td>
<td>No/recovery</td>
<td>Arend et al. (2004)</td>
</tr>
<tr>
<td>61/M</td>
<td>Pulmonary</td>
<td>Pred, MTX, Lefl, Infl</td>
<td>No/recovery</td>
<td>Hage et al. (2003)</td>
</tr>
<tr>
<td>67/F</td>
<td>Meninges</td>
<td>Pred, MTX, Infl</td>
<td>No/recovery</td>
<td>Muñoz et al. (2007)</td>
</tr>
<tr>
<td>82/F</td>
<td>Pulmonary/ meninges</td>
<td>Pred</td>
<td>7/Death</td>
<td>Tajiri et al. (2009)</td>
</tr>
<tr>
<td>80/M</td>
<td>Leather/disseminated</td>
<td>MTX, Pred</td>
<td>ERC/death</td>
<td>Diaz et al. (2010)</td>
</tr>
<tr>
<td>74/M</td>
<td>Skin</td>
<td>Pred</td>
<td>DM2/recovery</td>
<td>Moosbrugger et al. (2008)</td>
</tr>
<tr>
<td>58/F</td>
<td>Skin</td>
<td>MTX, HXQ, Adal</td>
<td>Trauma</td>
<td>Morgan et al. (2008)</td>
</tr>
<tr>
<td>45/F</td>
<td>Brain-meninges</td>
<td>MTX, Pred</td>
<td>DM2 de novo/treatment</td>
<td>Threshing et al. (2012)</td>
</tr>
<tr>
<td>70/M</td>
<td>Brain-meninges</td>
<td>Infl, Ritux, Pred, MTX</td>
<td>None</td>
<td>Wingfield et al. (2011)</td>
</tr>
<tr>
<td>Average age: 63.8</td>
<td>Pulmonary: 50%</td>
<td>MTX: 75%; Pred: Infl 75%; Lefl: HXQ 16%; 16%;</td>
<td>DM2: 16%; ERC: 8.3%</td>
<td>Percentage of patients according to variables</td>
</tr>
<tr>
<td>Skin: 16%</td>
<td>Meninges: 16%</td>
<td>Adal: Biological 8.3%; 66%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disseminated: 8.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adal: adalumab; 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

---


Carlos Abud-Mendoza * Marco U. Martínez-Martínez

Unidad Regional de Reumatología y Osteoporosis, Hospital Central “Dr. Ignacio Morones Prieto” y Facultad de Medicina de la Universidad Autónoma de San Luis Potosí, San Luis Potosí, S.L.P., México

* Autor para correspondencia.

E-mail address: c_abud@hotmail.com (C. Abud-Mendoza).
20 mg/dl, protein of 111 mg/dl, WBC 14 mm³, 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. 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).

**References**


Ramiro F. Trillos, a Daniel Gerardo Fernández-Ávila,b,* María C. Díaz,b Juan M. Gutiérrezb

a Departamento de Neurología, Hospital Universitario San Ignacio, Pontificia Universidad Javeriana, Bogotá, Colombia

b Unidad de Reumatología, Hospital Universitario San Ignacio, Pontificia Universidad Javeriana, Grupo Javeriano de Investigación en Enfermedades Reumáticas, Bogotá, Colombia

*Corresponding author.

E-mail address: danielfernandezmd@gmail.com

(D.G. Fernández-Ávila).

---

**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 reumatoidea: 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 8.76,7 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 was a 77-year-old woman who had RA treated with methotrexate 7.5 mg/week 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