MedicalExpress

LETTER TO THE EDITOR

Rapid progression of neurotoxoplasmosis in a patient with concomitant rheumatoid arthritis and systemic lupus erythematous

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Oliveira MF, Pereira CB, Silva VB Costa MC, Paes VR, El-Ibrahim R. Rapid progression of neurotoxoplasmosis in a patient with concomitant rheumatoid arthritis and systemic lupus erythematous. MedicalExpress (São Paulo, online). 5:ml18002

Received for Publication on December 21, 2017; **First review** on January 30, 2018; **Accepted for publication** on February 25, 2018; **Online on** March 16, 2018

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Dear Editor

Toxoplasmosis is one of the most common human infections. About one-third of the entire world population is infected with latent toxoplasmosis.[1-6] Central nervous system (CNS) toxoplasmosis occurs due to reactivation of previous latent infection. Patients usually present with fever, headache, impaired consciousness, seizures, and/or focal neurological deficits.[1-5]

CNS toxoplasmosis may complicate the clinical course of patients with acquired human immunodeficiency (e.g. AIDS), immune system disease, or prolonged pharmacologic immunosuppressive treatment.[1-5] Because the clinical picture and diagnosis are challenging, neurotoxoplasmosis may mimic several other CNS disorders, being especially difficult to manage and frequently requiring empiric treatment.[1-5]

We present an unusual case of neurotoxoplasmosis developing in a patient with concomitant rheumatoid arthritis and systemic lupus erythematous (SLE).

CASE DESCRIPTION

History. A 60-year-old female patient complaining of progressive holocranial headache for 60 days, worsening two days before admission to hospital. Additionally she reported daily nausea and vomiting. Fever was absent. Her physical examination revealed a central facial paresis at left and typical articular deformities in feet, hands and knees, suggestive of rheumatoid arthritis.

She had been treated for rheumatoid arthritis and systemic lupus erythematous for 37 years: currently, she was in use of Prednisone 5mg/day; Levotiroxine 50mcg/day; aspirin 100mg/day and sertraline 50mg/day. She discontinued some of the medications 2 weeks before admission to Hospital, maintaining only levothyroxine and sertraline.

She had already used chloroquine, methotrexate and leflunomide years before. She discontinued use of chloroquine due to corneal abrasion; methotrexate and leflunomide were discontinued due to digestive symptoms five years before.

Imaging results. Computerized tomography and magnetic resonance revealed multiple nodular images of different sizes in the supratentorial cortex, especially in the cortico-subcortical interface, with vasogenic edema. There was contrast enhancement in the lesions: initially this was peripheral, but became homogeneous in a late phase (Figure 1). Angiographic images obtained through MR were normal, without signs of vasculitis in the entire intracranial arterial circulation. No signs of sinus thrombosis. Perfusional evaluation revealed increased blood flow and capillary permeability in all lesions. Spectroscopy displayed increased choline peak, decreased n-acetyl-aspartate (NAA) peak, as well as an increase in the lipid/lactate peak.

To rule out other putative causes, the patient was submitted to abdominal and thoracic CT, both resulting

DOI: 10.5935/MedicalExpress.2018.ml.002

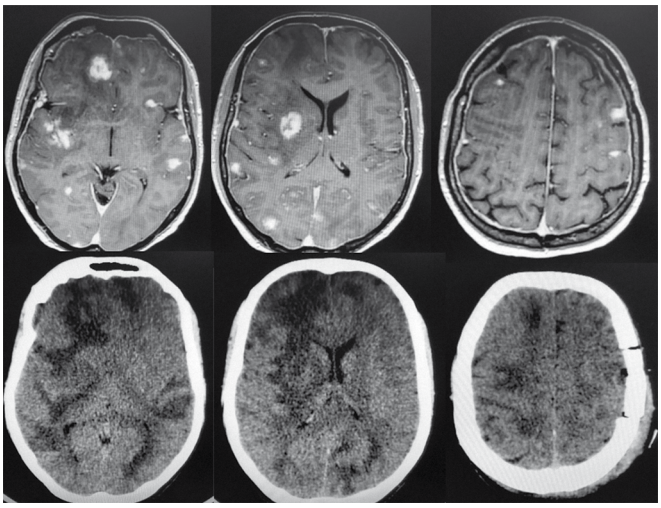

Figure 1. Magnetic resonance (MR) and computed tomography (CT) images displaying multiple cortical and subcortical parenchymal lesions, with enhancement after contrast infusion. Although it is a typical radiological presentation for neurotoxoplasmosis, it is also not specific.

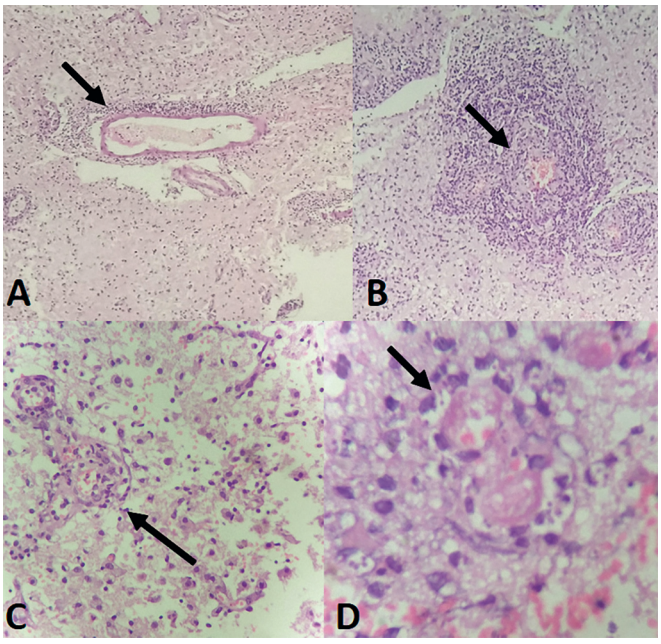

Figure 2. Histology image in hematoxilin-eosin. From A to D, different degrees of image magnification. It is possible to see the lymphocytic cells surrounding areas of suppurative presentation containing tachyzoites (arrows).

normal. Breast and thyroid ultrassonographic evaluations were also normal. Endoscopic investigation was eventless. Cerebrospinal fluid analysis was fairly typical for viral meningitis: 62 cells (71% lymphocytes; 10% macrophages; 3% neutrophils; 16% monocytes), protein 410 mg/dL and glucose 174 mg/dL. Laboratorial tests were normal. C-reactive protein (2.07 mg/L) and hemosedimentation velocity (6 mm/h) were normal. Investigation for proteins C and S, antithrombin III, lupic anticoagulant were negative. Serologic tests were negative for HIV, Hepatitis B and C.

At this point an open brain biopsy was proposed. Surgery was uneventful.

Pathology. Macroscopic pathological examination revealed cerebral parenchyma with a perivascular lymphocytic pattern and reparative gliosis. There were marked suppurative areas, in which Toxoplasma gondii tachyzoites were identified. Immunohistochemistry revealed positivity to *Toxoplasma gondii* antibodies (Figure 2). No signs of granulomas or neoplasms were found.

Post-operative. In the second post-operative day the patient had impaired consciousness and developed acute respiratory failure, requiring intubation and ventilatory support. She progressively deteriorated, developed pneumonia and had severe sepsis, with multiple organ dysfunction. We introduced pyrimethamine and sulfadiazine but at the seventh post-operative day, in spite of all of the adopted measures, her pupils became middle sized and fixed, with no brainstem reflexes and she died due to refractory intracranial hypertension.

DISCUSSION

Table 1 summarizes similar cases previously reported. Here we report an unusual presentation of neurotoxoplasmosis in a middle aged white woman harboring both rheumatoid arthritis and SLE. Although her previous medical history showed use of immunosupressors (leflunomide, methotrexate and prednisone), she developed a rapid progression of CNS neuroinfection without current immunosuppression therapy.[1-5] We believe that surgical procedure did not change clinical course of disease however was important to identify etiological agent.

Toxoplasma gondii infection is a common disease worldwide. Acute infection in an immunocompetent host is usually asymptomatic. In immunodeficient patients, cerebral toxoplasmosis may develop with 3 major pathologic patterns, which are diffuse encephalopathy with or without seizures, meningoencephalitis, and singular or large progressive mass lesions. Definitive diagnosis may require the presence of Toxoplasma antibodies in serum. In some doubtful cases, brain biopsy can provide a definitive diagnosis.[1-5]

A relationship between rheumatoid arthritis and SLE with opportunistic infections, including toxoplasmosis in its cerebral form has been reported.[1-5] Nardone et al.[2] reported the development of cerebral toxoplasmosis in a patient under treatment with adalimumab for rheumatoid arthritis. Lassoued et al.[3] documented two cases of toxoplasmic chorioretinitis following anti-TNF alpha treatment (with adalimumab, infliximab and etanercept) for rheumatoid arthritis. Cerebral toxoplasmosis associated with immunosuppressive medication has been reported by Safa et al.[4] and Nakamura et al.[5]

Young et al[1] reported a case of cerebral toxoplasmosis in a patient receiving multiple immunosuppressive medications, including methotrexate, infliximab, prednisone and leflunomide

Table 1. Data of published cases of cerebral toxoplasmosis after imunosupression drugs.

Author (Year)	Age	Gender	Disease	Medication	Outcome
Young (2005)	36	Female	RA	Methotrexate, infliximab, prednisone and leflunomide	Improved
Nardone (2014)	67	Male	RA	Adalimumab	Good clinical response
Lassoued (2007)	41 40	Male Female	RA RA	Adalimumab, infliximab and etanercept	Opthalmic sequalae of chorioretinitis Good response
Safa (2013)	71	Female	CNV and type I essential cryoglobulinemia	Rituximabe	Cognitive impairment
Nakamura (2005)	44	Female	Behcet disease	Ciclosporine monotherapy	Asymptomatic
Pulivarthi (2015)	76	Female	RA	Metotrexate and infliximab	Improved
Pistachii (2016)	48	Female	Undifferentiated connective disease	Mycophenolate Mofetil	Improved
Pagalavan (2011)	18	Female	SLE	Methylprednisolone	Improved

SLE = systemic lupus erythematous; RA = rheumatoid arthritis; CNV = cutaneous necrotizing vasculitis.

for rheumatoid arthritis[1]. Pulivarthi et al.[6] described a case of 76 year old woman with methotrexate and infliximab. Pistacchi et al[7] described a case of 48 year old woman with Mycophenolate Mofetil. Pagalavan et al[8] reported a case of a 18 year old woman after intravenous methylprednisolone.

Thus, all the authors here presented propose that cerebral toxoplasmosis should be considered in the differential diagnosis of patients receiving immunosuppressive medications, such as methotrexate, rituximab, adalimumab and infliximab, who present with neurological manifestations.[1-5]

Although scarcely represented in literature in the form of case reports, it seems clear that there is a potential risk of toxoplasmosis activation in patients requiring immunosuppression treatments in the context of rheumatoid arthritis and SLE, either in acute or in chronic presentation.[1-5] Such patients should be screened for toxoplasmosis before starting medication and should also be screened in routine control evaluations. Moreover, due to its severity and potential lethal evolution, neurotoxoplasmosis should be empirically treated in the presence of unexpected neurological symptoms in such patients, while other causes are simultaneously investigated. Knowledge of the patient's seropositive status helps close monitoring and the ability to provide early treatment, if necessary.

AUTHOR PARTICIPATION

Matheus Fernandes de Oliveira and Cristiana Borges Pereira designed paper, collected and analyzed data, wrote paper and made final review.

Vitor Brito Silva and Maristela Carvalho Costa designed paper, collected and analyzed data and made final review.

Vitor Ribeiro Paes and Roberto El Ibrahim analyzed pathological findings, discussed clinical and image findings and made final review of paper.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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