Case report

Fatal cryptococcal meningitis in a juvenile lupus erythematosus patient

Erica G. Cavalcantea, João D. Montonib, Guilherme T. Oliveiraa, Lucia M.A. Camposb, Jose A. Paz, Clovis A. Silvaa,*

aUnit of Pediatric Rheumatology, Instituto da Criança do Hospital de Clínicas da Faculdade de Medicina da Universidade de São Paulo (ICr-HC-FMUSP), São Paulo, SP, Brazil
bUnit of Pediatric Nephrology, Instituto da Criança do Hospital de Clínicas da Faculdade de Medicina da Universidade de São Paulo (ICr-HC-FMUSP), São Paulo, SP, Brazil

A B S T R A C T

Cryptococcosis is a fungal infection caused by Cryptococcus neoformans, generally associated with immunodeficiency and immunosuppressive agents, and it is rarely reported in systemic lupus erythematosus (SLE), particularly in juvenile SLE (JSLE). From January 1983 to June 2011, 5,604 patients were followed at our University Hospital and 283 (5%) of them met the American College of Rheumatology (ACR) classification criteria for SLE. Only one (0.35%) of our JSLE patients had cryptococcal meningitis and is described in this report. A 10-year old girl was diagnosed with JSLE. By the age of 15 years, she presented persistent headaches, nausea and vomiting for a 5 day period without fever, after a cave-exploring trip. At that moment, she was under 10 mg/day of prednisone, azathioprine and hydroxychloroquine. A lumbar puncture was performed and India ink preparation was positive for cryptococcosis, cerebrospinal fluid culture yielded Cryptococcus neoformans and serum cryptococcal antigen titer was 1:128. Azathioprine was suspended, and liposomal amphotericin B was introduced. Despite of treatment, after four days she developed amaurosis and fell into a coma. A computer tomography of the brain showed diffuse ischemic areas and nodules suggesting fungal infection. Four days later, she developed severe sepsis and vancomycin and meropenem were prescribed, nevertheless she died due to septic shock. In conclusion, cryptococcal meningitis is a rare and severe opportunistic infection in juvenile lupus population. This study reinforces the importance of an early diagnosis and prompt introduction of antifungal agents, especially in patients with history of contact with bird droppings.

© 2014 Elsevier Editora Ltda. All rights reserved.
Meningite criptocócica fatal em paciente com lúpus eritematoso sistêmico juvenil

RESUMO

Cryptococose é uma infecção fúngica causada pelo Cryptococcus neoformans, geralmente associada com imunodeficiências e drogas imunossupressoras, e foi raramente descrita em pacientes com lúpus eritematoso sistêmico (LES), particularmente em LES juvenil (LESJ). De janeiro de 1983 a junho de 2011, 5.604 pacientes foram seguidos em nosso Hospital Universitário e 283 (5%) casos preencheram critérios de classificação diagnóstica do Colégio Americano de Reumatologia para LESJ. Apenas um (0.35%) destes apresentou meningite criptocócica. Esta paciente teve diagnóstico de lúpus aos 10 anos de idade. Aos 15 anos, ela apresentou cefaleia, náuseas e vômitos durante 5 dias, sem febre, após viagem à regiãode cavernas. Neste momento, ela estava em uso de prednisona 10 mg/dia, azatioprina e hidroxicloroquina. Foi realizada punção lombar e a tinta da Índia foi positiva para cryptocoque, a cultura do líquido cerebroespinhal também foi positiva para Cryptococcus neoformans e a pesquisa de antígeno criptocócico sérico foi positiva em título de 1:280. Azatioprina foi suspensa e anfotericina B liposomal (3 mg/Kg/dia) foi iniciada. No entanto, quatro dias após ela desenvolveu amrause e coma. A tomografia computadorizada de crânio demonstrou áreas isquêmicas e nódulos sugestivos de infecção fúngica. Após quatro dias, ela desenvolveu sepse grave e vancomicina e meropenem foram iniciados, entretanto foi o óbito devido choque séptico. Portanto, meningite criptocócica foi uma rara e grave infecção oportunista em uma população de lúpus juvenil. Este estudo reforça a importância do diagnóstico precoce e da pronta introdução de agentes antifúngicos, principalmente em pacientes com história de contato com excrementos de pássaros.

© 2014 Elsevier Editora Ltda. Todos os direitos reservados.

Introduction

Infections are frequently observed in systemic lupus erythematosus (SLE) patients with high morbidity and mortality rates, and bacteria, virus, protozoa and fungi are considered the main cause.¹ ²

Cryptococcosis is a fungal infection caused by Cryptococcus neoformans, associated generally with primary or secondary immunodeficiency and with immunosuppressive agents.³ The central nervous system (CNS) is the most common site of infection,² with insidious and non-specific signs and symptoms of meningitis.⁴ Worthy of note, cryptococcal infection is rarely reported in adults with SLE,⁵⁻¹⁰ especially in juvenile SLE (JSLE) patients.⁴ ⁸

From January 1983 to June 2011, from 5,604 patients in follow-up at the Pediatric Rheumatology Unit of the Instituto da Criança da Faculdade de Medicina da Universidade de São Paulo, 283 (5%) of them met the American College of Rheumatology (ACR)¹¹ classification criteria for SLE. Only one (0.35%) of our JSLE patients had cryptococcal meningitis and is described herein. This study was approved by the Local Ethics Committee of our University Hospital.

Case report

A 10-year old girl was diagnosed with JSLE based on malar rash, photosensitivity, oral ulcers, antinuclear antibodies (ANA) (1/200, dense fine speckled pattern), and the presence of anti-double-stranded DNA (anti-dsDNA) and anti-Sm antibodies, fulfilling the ACR classification criteria for SLE.¹¹ At that moment, her SLE Disease Activity Index 2000 (SLEDAI-2K)¹² was 6 and she was treated with prednisona (2.0 mg/kg/day), progressively diminished to 10 mg/day, and hydroxychloroquine. At the age of 14, she was hospitalized due to arthritis in the knees, malar rash, cutaneous vasculitis (tender finger nodules in hands and lower limbs) and arterial hypertension. Her laboratory exams revealed hemoglobin 11.5 mg/L, hematocrit 34%, white blood cell count 7,200/mm³ (84% neutrophils, 8% lymphocytes, 1% eosinophils and 7% monocytes), platelets 180,000/mm³, proteinuria (0.5 g/24h), abnormal urinalysis (81,000 leukocytes/mL, 21,000 erythrocytes/mL and granular casts), urea 52 mg/dL (normal 10-42), creatinine 0.8 mg/dL (normal 0.6-0.9), C3 0.15mg/dL (normal 0.5-1.8) and C4 0.01 mg/dL (normal 0.1-0.4). The erythrocyte sedimentation rate was 33mm/1º hour and C-reactive protein 7.9 mg/dL (normal < 5). Immunological tests showed positive anti-dsDNA and negative lupus anticoagulant, IgG and IgM anticardiolipin antibodies, and her SLEDAI-2K was 32. Renal biopsy showed diffuse proliferative lupus nephritis (class IV of the World Health Organization - WHO classification). She was treated with three pulses of intravenous methylprednisolone associated with seven monthly sessions of intravenous cyclophosphamide (IVCYC (0.5-1.0 g/m²/month)) following this treatment every 3 months for six months. At the age of 15 years, she was treated with azathioprine (3.0 mg/kg/day).

After 3 months, she displayed persistent headaches, nausea and vomiting for 5 days, that started twenty days after a trip to a cave region in the rural zone of São Paulo state, Brazil. She was promptly hospitalized due to severe headache, vomiting, lethargy, arterial hypertension and nuchal rigidity. She...
did not have fever. At that moment, she was under 10 mg/day of prednisone, azathioprine and hydroxychloroquine. Laboratory tests revealed hemoglobin 13.3 mg/L, hematocrit 40%, white blood cell count 10,300/mm³ (94% neutrophils, 2% lymphocytes and 4% monocyte), platelets 127,000/mm³, proteinuria (1.25 g/24h), urea 48 mg/dL, creatinine 0.6 mg/dL, C3 0.6 mg/dL and C4 0.09 mg/dL. Immunological tests were negative for anti-dsDNA, lupus anticoagulant, and IgG and IgM anticardiolipin antibodies. The SLEDAI-2K was 6. A lumbar puncture was performed with opening pressure of 48 cm H₂O and cerebrospinal fluid (CSF) analysis showed a white blood cell count of 500/mm³ (mononuclear cells 26% and neutrophils 74%), hyperproteinorrhachia (66 mg/dL) and hypoglycorrhachia (16 mg/dL in CSF to 94 mg/dL in serum). A CSF India ink preparation was positive for Cryptococcus, CSF culture yielded Cryptococcus neoformans and serum cryptococcal antigen titer (16 mg/dL in CSF to 94 mg/dL in serum). A CSF India ink preparation showed diffuse ischemic areas and periventricular nodules suggesting fungal infection. After four days, she presented fever, bacterial pneumonia and severe sepsis. Vancomycin was promptly introduced. However, despite this treatment, four days later she developed amaurosis with vision loss. The increased opening pressure upon lumbar puncture was 50 cm H₂O. The brain CT scanning showed diffuse ischemic areas and nodules suggesting fungal infection. After four days, she presented fever, bacterial pneumonia and severe sepsis. Vancomycin and meropenem treatment started and she required invasive mechanical ventilation. She died due to septic shock three days later.

Discussion

We reported a single case of fatal cryptococcal meningitis in a large population of JSLE, showing the rare frequency of this fungal infection. Importantly, in all of our lupus patients with clinical signs and symptoms of meningitis, we promptly have been indicated brain CT scanning and CSF analysis. In our Pediatric University Hospital, routine evaluation of CSF in all JSLE patients with the above clinical findings include an India ink preparation.

Cryptococcosis is a life-threatening fungal infection caused by Cryptococcus neoformans, acquired mainly by inhalation of aerosolized particles, associated with birds droppings, particularly pigeon, and bats droppings. This infection is habitually insidious and its symptoms range from asymptomatic disease, limited to the lung, to severe infection, as observed in our case. Almost all symptoms of cryptococcal meningitis such as headaches, vomiting and nausea, are nonspecific and so it could be confused with active CNS manifestation of lupus. Our patient presented persistent and severe headaches, associated to vomiting and meningeal sign, which led to the suspicion of CNS infection even when clinically afebrile, with prompt diagnose and treatment. However, the five days prior to the onset of symptoms certainly were decisive to the unfavorable outcome.

Worthy of note, is that high mortality by this fungal infection has been described in immunosuppressed patients, such as adult and pediatric lupus erythematosus patients. The main predisposing factors for symptomatic and severe infection were the use of steroids and immunosuppressive agents (especially cyclophosphamide and azathioprine) and a high SLEDAI score, as observed herein. Likewise, intrinsic immunological abnormalities in humoral and cellular function seen in lupus patients may contribute to this opportunistic infection.

The elevated opening pressure upon lumbar puncture and CSF analysis found in this infection is rather similar to tuberculosis and viral meningitis. Remarkably, the diagnosis of Cryptococcus neoformans meningitis should be confirmed by the identification of this fungi in Indian ink preparation and/or by a positive culture in CSF analysis. Additionally, cryptococcal antigen in the blood or CSF may help the diagnosis. Intracranial massive lesions may also be evidenced in CNS of these patients, as observed in the brain CT scan of the present case.

The treatment of CNS cryptococcosis includes amphotericin B alone or associated with flucytosine. The mechanisms of these drugs are disruption of fungal cell membrane and inhibition of fungal DNA and protein synthesis, respectively. Death due to this cryptococcal meningencephalitis in SLE is rare in the literature. The main causes of mortality in SLE with this infection are meningitis and septic shock, as evidenced in our case. Unfortunately, the family did not give permission to perform necropsy.

In conclusion, cryptococcal meningitis is a rare and severe opportunistic infection in pediatric lupus population. This study reinforces the importance of an early diagnosis and prompt introduction of antifungal agents, especially in patients with history of contact with bird droppings.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

This study was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo - FAPESP (grant #08/58238-4 to CAS) and by CNPQ (302724/2011-7 to CAS), Federico Foundation to CAS and by Núcleo de Apoio à Pesquisa “Saúde da Criança e do Adolescente” da USP (NAP-CriAd).

References


