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Case Report

Granulomatous Amoebic Encephalitis Caused by *Acanthamoeba* in a Patient with Systemic Lupus Erythematosus

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Abstract: A 25-year-old chronically immunosuppressed woman with systemic lupus erythematosus (SLE) died after developing subacute granulomatous encephalitis caused by *Acanthamoeba*. Amoebic trophozoites were also found in the lung, suggesting a primary pulmonary focus of infection. The infectious encephalitis was difficult to differentiate from a flare-up of central nervous system lupus. This case illustrates that *Acanthamoeba* can cause fatal encephalitis in lupus patients, as well as in patients with acquired immunodeficiency syndrome as previously reported. To our knowledge, this is the first reported case of granulomatous amoebic encephalitis due to *Acanthamoeba* in a patient with SLE.

Keywords: *Acanthamoeba*; Granulomatous amoebic encephalitis; Opportunistic Infection; Systemic lupus erythematosus

Introduction

Recent progress in our understanding of lupus has resulted in a prolonged life expectancy for patients. In the 1980s, 15-year survival rates from the onset were reported to be 83.2 ± 7.4% even in patients with lupus nephritis which has one of the most unsatisfactory outcomes of any of the lupus subsets [1]. This improvement in prognosis was associated with 15 years of progress in the management lupus. The newer therapeutic approaches include high-dose oral steroids, steroid pulse, azathioprine (AZ), cyclophosphamide (CY) and dialysis. Because of long-term aggressive therapy, infection is the most common cause of death in systemic lupus erythematosus (SLE) patients. SLE patients infected with *Pneumocystis*, *Nocardia*, *Cryptococcus* and *Toxoplasma* have been reported [2–4].

Free-living amoebae, such as *Acanthamoeba*, may behave as opportunistic microorganisms, usually afflicting immunocompromised individuals, which may cause granulomatous amoebic encephalitis. From 1984, these opportunistic infections have been described in more than 10 patients with acquired immunodeficiency syndrome [5,6].

Recently, we experienced a fatal case of amoebic encephalitis in a patient with SLE. To the best of our knowledge, this is the first well-documented case of granulomatous amoebic encephalitis caused by *Acanthamoeba* in a patient with SLE.

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Case Report

A 25-year-old woman was admitted for the third time to Saitama Medical Center on 28 August 1993, because of a low-grade fever and transient loss of consciousness.

She had been well until age 12 years, when she developed polyarthralgia and facial erythema. She went to another hospital, where various medical evaluations were performed. The blood test reportedly showed leukopenia and lymphopenia. The urine test was positive for protein and sugar and the sediment contained numerous red blood cells. Serum complement levels, including C3 and C4, were decreased. Tests for antinuclear antibody (ANA) and for antibody to

double-stranded (ds) DNA were positive. A diagnosis of SLE was made. Subsequently, she was treated with prednisone (20–60 mg/day). AZ (50–100 mg/day) was added in October, 1987. Four years before admission (November 1989), the patient developed Herpes zoster. She contracted sepsis with pneumonia due to *Listeria monocytogenes* in January 1991. In June 1991, AZ was discontinued, and she was then receiving CY (50–100 mg/day) until her final admission.

On 28 August 1993, she was found unconscious in the car park of a market. She was immediately transferred to the Saitama Medical Centre. Her temperature was 37.5°C, pulse 60/min and respirations 16/min. Her blood pressure was 150/76 mmHg. During the examination, the patient was awake but confined to a wheelchair. She appeared chronically ill and cushingoid. Numerous discoid eruptions were noted to involve the face, mainly the nose and right ear, and the extremities. The neck was supple. On neurological examination, the patient was alert and oriented, with fluent speech and comprehension; the cranial nerves were normal. Other neurological tests were normal, apart from a slightly decreased deep tendon reflex in the right lower extremity. Urine was negative for protein and sugar. Haemoglobin was 11.2 g/dl and the white blood cell count 11 600/mm^3, with 1% metamyelocytes, 39% stab neutrophils, 51% segmented neutrophils, 8% lymphocytes and 1% monocytes. The platelet count was 223 000/mm^3 and the erythrocyte sedimentation rate 38 mm/h. The levels of serum electrolytes, renal and liver function and fasting lipids were within normal limits, although the level of serum albumin was decreased. The serum complement levels were CH50 26.2 U/ml (normal range: 30–45), C3 67 mg/dl (65–95) and C4 29.8 mg/dl (20–30). Tests for ANA and antibodies to SSA and Sm were positive but those to dsDNA, single-stranded DNA, RNP and SSB were all negative. Rheumatoid factor was negative and C-reactive protein was 1.6 mg/dl. Total serum IgG was 1380 mg/dl, IgA 256 mg/dl and IgM 12 mg/dl. The CD4+/CD8+ ratio of lymphocytes was 0.2. Tests for serum human immunodeficiency virus antibody and anticardiolipin antibody were negative. The cerebrospinal fluid (CSF) was clear and acellular; the opening pressure was 160 mmH_2O, protein 66 mg/dl and glucose 42 mg/dl. Cultures of the CSF, blood and urine were negative. A cranial computed tomography scan was unremarkable. The patient remained afebrile and the blood pressure was stable after admission.

On the second hospital day, she developed sudden loss of consciousness with generalised convulsion. The laboratory data were unchanged compared with those obtained on admission. Intravenous methylprednisolone pulse therapy of 1000 mg/day was given for suspected central nervous system (CNS) lupus. On the third hospital day, the patient complained of headache. On the following day, urinary incontinence developed.

On the sixth hospital day, the patient became febrile and slurred speech and disorientation developed. A T1-weighted magnetic resonance image of the brain disclosed a slightly low signal intensity area in the right frontal region, suggesting an intracranial mass. Axial and sagittal T2-weighted images at this level showed abnormally high signal intensity and enhancement (Fig. 1).

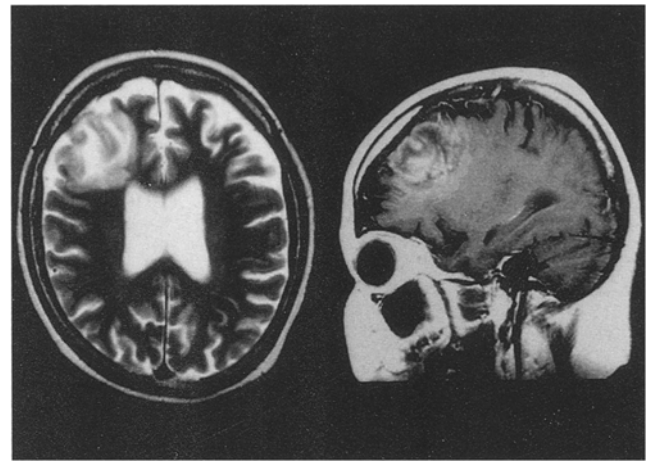

Fig. 1. Axial (left) and sagittal (right) postcontrast T2-weighted images demonstrate striking enhancement with high signal intensity of an inhomogeneous mass in the right frontal lobe.

On the 14th hospital day, cranial angiography was performed but neither a thrombus nor an aneurysm was seen. The patient's condition gradually deteriorated. Emergency craniotomy was performed for decompression. The brain biopsy specimens taken at craniotomy were tentatively reported to represent cryptococcal encephalitis which was treated with amphotericin B. Despite aggressive therapy, she died on the 29th hospital day because of multiple organ failure.

A specimen, which had been obtained from the right frontal lobe by open biopsy on the 14th hospital day, revealed complete obliteration of normal cerebral tissue and replacement with markedly increased numbers of glial cells. A perivascular infiltrate consisting of neutrophils, lymphocytes, histiocytes and giant cells was also observed. Numerous foci of small vessel vasculitis were recognised. The lumina of small vessels were filled with fibrin thrombi and areas of mural fibrinoid degeneration were seen. Small globoid bodies were detected in many histiocytes and giant cells. Free-living amoebae, both trophozoites and cyst forms, were seen throughout the brain tissue (Fig. 2a). Orthotoluidine-blue O staining showed the characteristic double wall of pentagonal cysts (Fig. 2b). The trophozoites were 15–20 μm in diameter, and the cysts 10–15 μm. Both the trophozoites and the cysts were uninucleate, and each nucleus contained a distinct, centrally located nucleolus. The pathological diagnosis of the biopsy specimen was granulomatous encephalitis due to *Acanthamoeba.*

At autopsy, the brain weighed 1350 g and showed marked anoxic degeneration. The microscopic examination findings were essentially the same as those of the biopsy specimen.

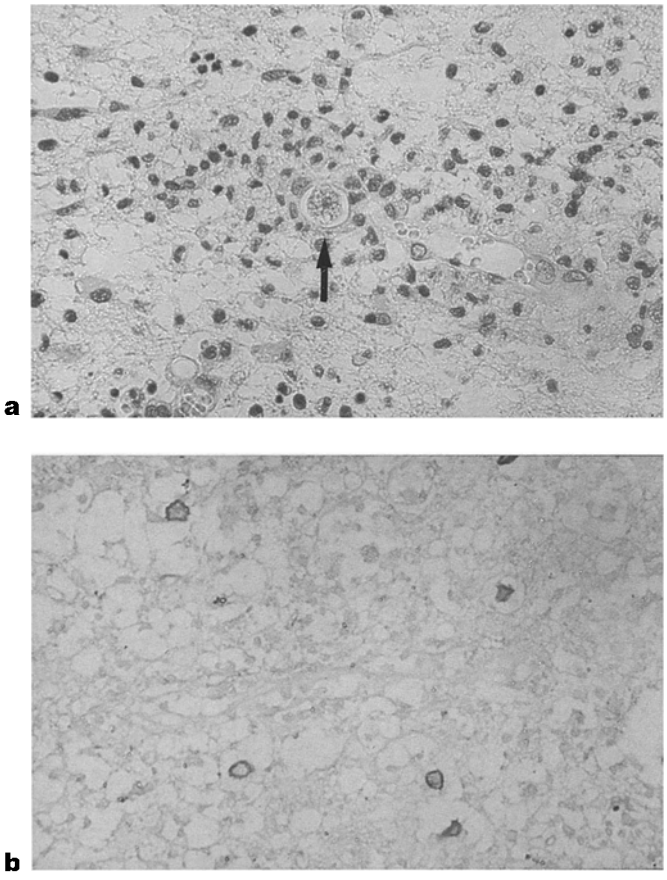

Fig. 2. (a) Granulomatous chronic encephalitis with glial cells, neutrophils, lymphocytes, histiocytes and giant cells. A representative amoebic trophozoite is readily recognisable (arrow) by its bubbly-appearing cytoplasm and small nucleus (H&E, original magnification ×400). (b) Typical morphological features of amoebic cysts are shown (orthotoluidine-blue O, original magnification ×400).

Pertinent microscopic examination results of other organs were:

1. Mild thickening of the glomerular capillary basement membrane, but no other significant renal changes compatible with membranous lupus glomerulonephritis.
2. Thickening of the alveolar septa due to the infiltration of inflammatory cells, especially in the upper lobe of the right lung, compatible with pneumonitis. A few amoebic trophozoites were seen within the ciliary alveolar epithelium of the lung (Fig. 3).
3. Congestion of the liver with mild periportal lymphoid cell infiltration.
4. Congestion of the spleen with mild perisplenitis.

Discussion

In our experience, the SLE mortality rate was 3.2% for the 10 years from 1985 to 1994. A significant decrease in the mortality rate is attributable to a reduction in uraemic

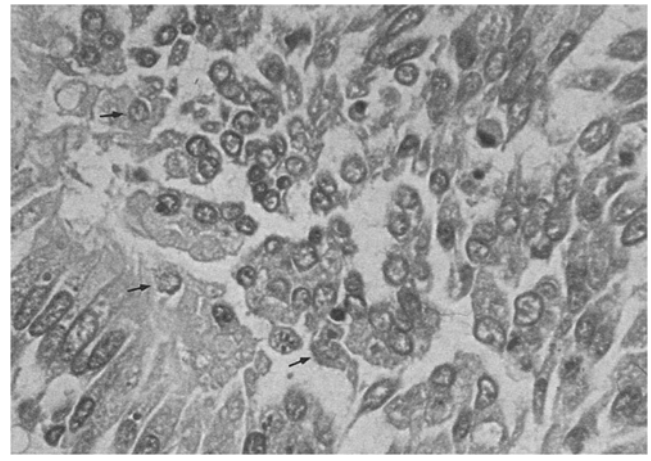

Fig. 3. Several amoebic trophozoites (arrows) are seen within the ciliary alveolar epithelium (PAS, original magnification ×200).

death. This reduction may be due to (1) a decreased number of lupus nephritis cases and/or (2) the beneficial effects of more aggressive therapy such as steroid pulse, immunosuppressants and dialysis for lupus nephritis. At the present time, CNS lupus and infection are the two main causes of death. The differentiation of CNS lupus from infection is difficult, especially in cases with CNS infection [7]. However, precise differential diagnosis of these conditions is of the utmost importance in selecting the proper therapy. It should be kept in mind, however, that the two conditions can coexist.

SLE patients with CNS infection have been reported. The infections manifest as meningitis or meningoencephalitis and the causative microorganisms include viruses, bacteria, *Cryptococcus* and *Toxoplasma*, as sources of opportunistic infection.

The diagnosis of amoebic encephalitis was established early in the course of hospitalisation by open biopsy in our case. As far as we know, however, there has reported to be no effective therapy for amoebic encephalitis. Slater et al. [8] reported that intravenous pentamidine is most suitable for the treatment of cutaneous *Acanthamoeba* infection before CNS involvement. We hesitated to administer the drug because of the evidence of CNS invasion and the side effect of nephrotoxicity. Further studies are needed to establish the optimal choice of therapy for amoebic encephalitis.

Acanthamoeba is a free-living amoeba that inhabits soil and fresh water. There are several different species and some have been isolated from debilitated or immunocompromised patients with opportunistic infection [5,6,9]. In our case, no history of exposure to contaminated fresh water was obtained. Accordingly, the route of infection and penetration into the brain must have been via haematogenous spread from the lung where amoebic trophozoites were present at autopsy.

This patient was at risk for opportunistic infection because she had been treated with steroids, AZ and CY. She had contracted Herpes zoster and *Listeria mono-*

cytogenes infections in the past. *Cryptococcus* is also known to cause meningitis but no *Cryptococcus* was detected in the autopsy specimens.

Grunnet et al. [10] reported amoebic meningoencephalitis due to *Acanthamoeba* in a patient with SLE. They identified *Acanthamoeba castellanii* as the causative organism, based on antisera to four species, but failed to identify a granulomatous lesion in the brain tissue. Grunnet's case showed a more fulminant course than our case and expired on the third hospital day. In this sense, our case is the first well-documented case of granulomatous *Acanthamoeba* encephalitis in a patient with SLE.

The precise diagnosis of CNS infection in patients with SLE is important because effective therapy for the causative microorganism is available. Every effort should be made to identify the microorganism using biopsy specimens and CSF samples. Applications of immunohistochemical and polymerase chain reaction methods may be promising alternatives as these diagnostic tools are sensitive and specific.

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