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Acanthamoeba meningoencephalitis presenting as neuropsychiatric lupus in a paediatric patient

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ABSTRACT

We present the case of a 16-year-old patient with systemic lupus erythematosus who presented with altered mental status and regressive behaviour. She was worked up and empirically treated for common and opportunistic infectious agents. All work-up was negative and after an extensive course of antibiotics she was treated for neuropsychiatric lupus with cytoxan. She initially responded, but this was short-lived and she eventually became comatose and passed away. On brain biopsy she was found to have numerous trophozoites with round nucleus, prominent nucleolus and thin nuclear membrane. Methenamine silver stain showed encysted amoeba, corresponding with a diagnosis of acanthamoeba meningoencephalitis. Making the diagnosis of acanthamoeba meningoencephalitis requires a high degree of suspicion. Specific serum antibodies may not be a reliable measure in immunocompromised patients and trophozoites in CSF can be confused with monocytes. Brain biopsy may be required to make a definitive diagnosis. It is important for clinicians treating immunocompromised patients to keep this agent in mind in an immunocompromised patient with neurological manifestations. Acanthamoeba infections have only been reported in a small handful of patients and, to our knowledge, this is the first reported case in the United States.

Introduction

Over the last five decades the prognosis of paediatric systemic lupus erythematosus (pSLE) has significantly improved. As survival rates improve, increasing attention is paid to mortality secondary to treatment related infections rather than the underlying disease. Sepsis secondary to community acquired pathogens and opportunistic infections have become the new leading cause of death in these patients (1).

Infections contribute significantly to the morbidity and mortality of children with SLE. The literature is replete with reports of patients on immunosuppressive medications that acquire opportunistic infections such as *Aspergillus, Candida, Nocardia, and pseudomonas* (1) While there are three cases of *acanthamoeba* infections described in adults with SLE, to our knowledge, there is only one other case described in pSLE (2-4)

Acanthamoeba is a free-living amoeba that can rarely cause life-threatening infections in both immunocompromised and immunocompetent patients. This report describes a second pSLE patient on immunosuppressive therapy who developed fatal granulomatous *acanthomoebic* meningoencephalitis. It illustrates the difficulty in differentiating neuropsychiatric lupus (NP-SLE) from infectious encephalitis.

Case report

A 16-year old African American female was diagnosed with SLE four years prior to presentation, who met criteria with a malar rash, arthritis, mucositis, and a positive ANA. She was treated with 20mg prednisone a day, 125mg imuran a day, and 300 mg plaquenil a day, but had a history of non-compliance.

She presented with nine days of headache, pharyngitis, nausea, vomiting and malaise, followed shortly by altered mental status, with regressive behaviour and an absence-like seizure. She was initially taken to an outside hospital where work-up was remarkable for lymphopenia (wbc 3600/mm^3, neutrophils 87%, lymphocytes 10%), anaemia (haematocrit 28.6g/dl) and hyponatermia (Na 123 mEq/l). Cerebrospinal fluid (CSF) had 3-4 wbc, 35 rbc, glucose of 41mg/dl and protein of 144 mg/dl. A cranial computed tomography (CT) scan was read as unremarkable. She was empirically treated with decadron, ceftriaxone, vancomycin and acyclovir. Her mental status deteriorated with disorientation and regression of behaviour. Encephalitis possibly superimposed on NP-SLE was suspected. CSF studies sent to the California Encephalitis Project were negative. She was transferred to Children's Hospital Los Angeles (CHLA) after she developed drooling, left-sided weakness and an oxygen requirement.

On admission to CHLA, the patient was oriented only to self and could not follow commands. She had photophobia, scleral icterus, diffuse crackles on lung exam, and clubbing with delayed cap-

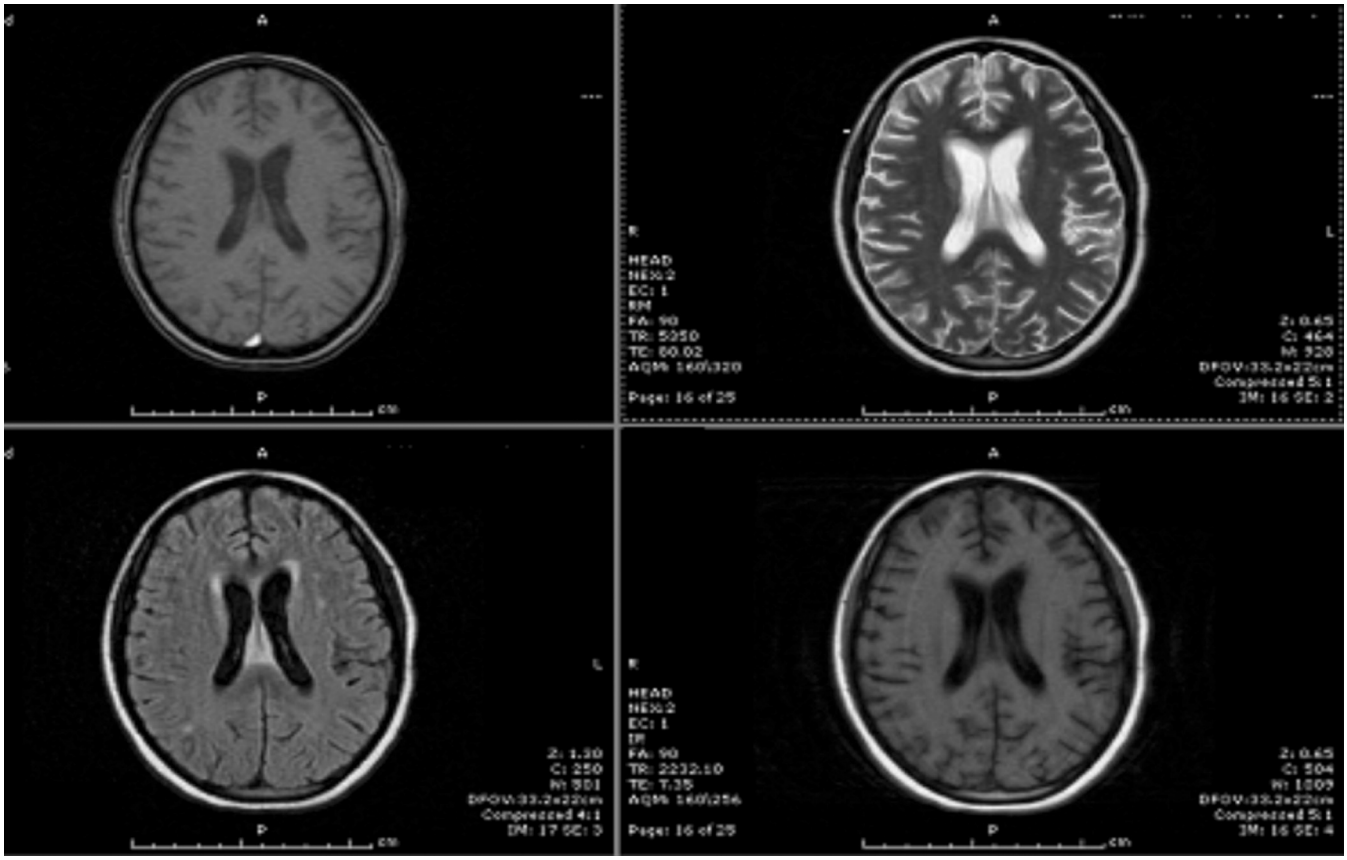

Fig. 1. MRI of the brain showing oedema in bilateral basal ganglia and the thalamus. There is persistent focal cerebral white matter lesions with increased signal in the midbrain and vermis, suggestive of progressive leukoencephalitis secondary to infection or lupus vasculitis.

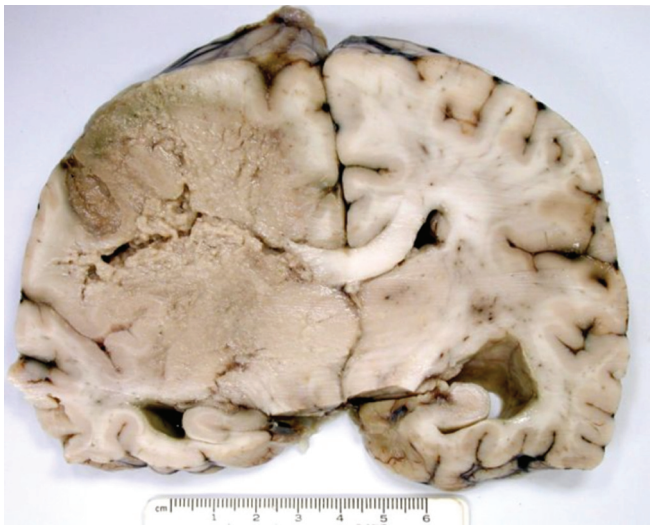

Fig. 2. Coronal section revealing right midline shift in the frontal and parietal lobes, as well as extensive granular necrosis.

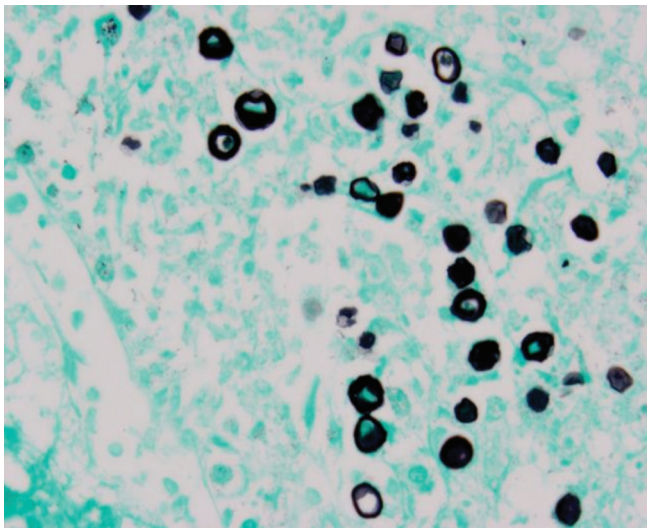

Fig. 3. Methenamine Silver stain showing encysted amoeba and their double capsule.

illary refill. She did not have any meningeal signs. Initial work-up showed pancytopenia (WBC 1200/mm^3, neutrophils 92%, lymphocytes 4%, haematocrit 29.1g/dl, 103,000 platelets mm^3), mild hyponatremia (sodium 132 mEq/l), elevated sedimentation rate of 127mm/hr, C-reactive protein of 0.7mg/dl and elevated creatinine of 1.2mg/dl. Pancreatic enzymes were mildly elevated (amylase 286U/L and lipase 517U/L). Complements were normal (C3 120mg/dl, C4 29mg/dl.), Double-stranded DNA was negative at 16. Anti-smith and anti-RNP were positive. Anti-ribosomal P and anti-neuronal antibody were negative. The extended antiphospholipid panel was negative. Urine protein to creatinine ratio was markedly elevated at 32. A renal biopsy was not done. A repeat CSF

was significant for an elevated protein of 413mg/dl and RBC of 46. MRI of the brain showed focal cerebral white matter lesions with increased signals in the midbrain involving the periaqueductal grey matter and the folia of the culmen vermis. The abnormalities suggested leukoencephalitis either due to infection or lupus vasculitis (Fig. 1). Nuclear medicine SPECT scan was normal. Chest x-ray showed atelectasis in the left lower lobe. The initial assessment was, SLE with pancytopenia, pancreatitis, lupus nephritis and NP-SLE versus infectious encephalitis.

Antibiotics were discontinued on admission except for the acyclovir, which was continued until herpes simplex virus PCR was negative. Azathioprine and hydroxychloroquine were held and she was started on methylprednisolone 25mg IV every eight hours. She continued to have increasing oxygen requirements. Chest CT showed a left lower lobe consolidation with air bronchograms and a wedge shaped atelectasis versus infarct in the right upper lobe with additional patchy infiltrates. Because of concern for community acquired pneumonia levofloxacin was started. Bronchoalveolar lavage (BAL) was done, and the culture showed a few coagulase negative staphylococci. Cytomegalovirus (CMV), Cryptococcus, legionella, mycoplasma, coccidiomycoses, mycobacterium avium, chlamydia, and pertussis, galactomannan B and fungal cultures were all negative.

Over the next 20 days the patient remained with altered mental status. Infectious work-up remained negative. Due to lack of improvement on the current treatment regimen it was decided that she be treated for NP-SLE with a three-day pulse of 1000 mg IV methylprednisolone and cyclophosphamide at 10mg/kg IV every two weeks. However, her mental status continued to wax and wane and she subsequently became combative and disoriented. Repeat MRI of the brain showed interval development of oedema in bilateral basal ganglia and the thalamus with persistent focal cerebral white matter lesions with increased signal in the midbrain and vermis, suggestive of progressive leukoencephalitis

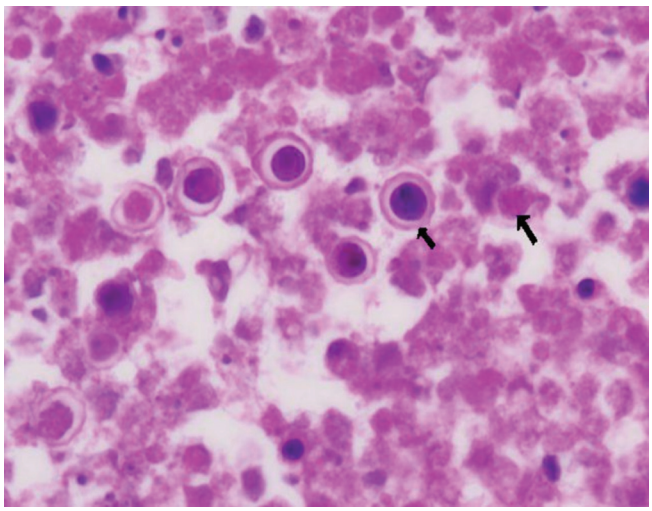

Fig. 4. H&E stain showing trophozoites with round nucleus prominent nucleolus and thin nuclear membrane (far right arrow) as well as numerous cysts (arrow on the left).

She was treated with gancyclovir for a positive quantitative CMV PCR and empirically with voriconazole for fungal infection. An additional dose of 1 gram IV of methylprednisolone was given followed by a maintenance dose of 30 mg every eight hours. After 19 days her respiratory status deteriorated with increasing oxygen requirement and hemoptysis, requiring mechanical ventilation. CT of the chest and abdomen showed an increase in bilateral lower lobe consolidation, with suspicion for pulmonary haemorrhage, enlarged kidneys, pancreatitis and multifocal colitis. Her antibiotic coverage was broadened to include mycofungin, meropenem, vancomycin and bactrim for 15 days. She improved and was eventually extubated. However after 7 days she deteriorated again with worsening mental status. A head CT was negative for bleed. Her second dose of cytoxan was given and over the next 7–10 days she began showing signs of improvement and was able to state her name and follow simple commands.

Because she improved with her immunosuppressive therapy a second attempt to discontinue antibiotics was made. However the patient again became febrile and meropenem was restarted. Her mental status worsened, she became withdrawn and her Glasgow coma score deteriorated to 3 requiring re-intubation. Head CT showed multiple large areas of oedema in the left frontal lobe and the left cerebellar hemisphere with interval worsening with shift to the left. These events subsequently lead to her demise on hospital day 59.

On autopsy, the brain weighed 1480 grams (normal for age 1000–1400 grams). Gross examination revealed brain oedema with extensive granular necrosis of left frontal and parietal cortex and white matter (Fig. 2). The microscopic examination revealed extensive cortical and white matter necrosis with inflammatory exudates including numerous macrophages. There were numerous trophozoites with round nucleus, prominent nucleolus and thin nuclear membrane (Fig. 4). There was no evidence of vasculitis. Methenamine silver stain showed encysted ameba (Fig. 3). The final neuropathological diagnosis was acanthamoeba meningoencephalitis, brain swelling with right midline shift, extensive necrosis, and transforamen magnum cerebellar herniation. There was no evidence of acanthamoebic infection in any other organ system. The renal pathology showed patent capillary lumen, diffuse glomerular mesangial hypercellularity and increase in the matrix in the cortex. No necrotising and/or sclerosing lesions in glomeruli were seen. The tubular, interstitial and vascular changes were insignificant and consistent with WHO class II lupus nephritis.

Discussion

The clinical manifestations of NP-SLE are often difficult to distinguish from infection. Both can present similarly with headache, change in mental status, and seizures. NP-SLE largely re-

mains a clinical diagnosis of exclusion because it lacks specific laboratory markers. Lumbar puncture results with opportunistic infections can be normal or similar to that of NP-SLE. Often a high index of suspicion is necessary to diagnose an opportunistic infection.

The most difficult CNS infections to discern are those secondary to tuberculosis, *pneumocystis jiroveci* and fungal and viral infections. These infectious etiologies can have an atypical, insidious onset and a diagnosis is often made only postmortem (7). Yang *et al*. noted that SLE patients with CNS infection not only had atypical clinical presentations but also atypical CSF findings with low white counts, usually less than ten (9). The uncharacteristic clinical and laboratory findings may be secondary to alterations in the immune system as a result of the administration of immunosuppressive agents and the immunologic dysfunction stemming from the disease itself (8).

CNS infections with *acanthamoeba* in SLE patients have been reported in adults (2-4). The only report in paediatric literature to date is by Lange *et al*. in Germany. They described a 16-year-old patient with a NP-SLE-like clinical picture who was treated for lupus flare. It was not until autopsy that *acanthamoeba* was discovered. This report primarily focused on the pathologic findings (16). To our knowledge, this is the first reported case of this infection in a pSLE patient in the United States.

In the last two decades, *acanthamoeba* has become recognised as a human pathogen causing serious and life-threatening infections. There are four clinical syndromes described: primary amoebic meningoencephalitis, amoebic granulomatous encephalitis (AGE), disseminated granulomatous amoebic disease and amoebic keratitis. AGE is caused by the *acanthamoeba* species, which has been isolated from water, soil and air in diverse geographic locations. AGE is most common in immunocompromised patients. Immunocompetent hosts eradicate amoebas by a complement-mediated attack. Thus, patients with active SLE and low complement levels are particularly at high risk of fatal infection (10, 11).

A high index of suspicion is necessary for the diagnosis of AGE as the clinical presentation can be insidious and diagnostic testing is unreliable. MRI and CT scan can show multifocal areas of signal intensity, or lesions indicating brain abscess or tumour suggestive of CNS infection (18). CSF studies can have a pleocytosis with lymphocytic predominance, elevated protein concentrations, decreased glucose and minimal cloudiness (17, 22). *Acanthamoeba* specific antibodies can also be measured in the patient's serum. However, in an immunocompromised individual, the immune system may not develop high enough titers (23, 24). Trophozoites can also be seen in the CSF after low speed centrifugation on a wet mount or on brain biopsy. Both of these require experienced examiners, as trophozoites can be difficult to distinguish from monocytes, polymorphonuclear leukocytes and macrophages (10, 11). CSF findings in NP-SLE can be variable and non-specific. At times there may be elevated levels of total protein, IgG, IgM, and IgA and the presence of oligoclonal bands (15). In addition, often the findings may be completely normal (14) limiting it's utility as a definitive diagnostic modality. However it remains important to perform a lumbar puncture and CSF analysis in a pSLE patient with CNS symptoms because of the need to assess for infection.

Since the diagnosis is difficult to make and most patients are diagnosed post mortem, there is no recommended treatment regimen. Current options include a combination of ketoconazole, fluconazole, sulfadiazine, pentamidine, isethionate, amphotericin B, azithromycin, itraconazole or rifampin (13, 17-19). Recent studies show that alkylphosphocholine compounds exhibit anti-acanthamoeba properties and the ability to cross the blood brain barrier (20, 21).

There are reports that suggest that early diagnoses may be the key to a successful outcome. Petry *et al*. described a case of a 64-year-old immunocompetent patient who was found to have trophozoites on CSF cytology. The patient was treated with fluconazole, rifampin, metronidazole and sulfadiazine for 14 days. The patient's symptoms resolved and CSF studies 4 weeks post-treatment were still negative. Singhal *et al*. reported three cases of immunocompetent children with AGE, two of which were successfully treated with trimethoprim-sulfamethoxazole rifampin and ketoconazole. Both of the patients on triple antibiotic therapy cleared the infection (12, 13).

In summary, it is difficult to differentiate between NP-SLE and opportunistic CNS infections with *acanthamoeba*. Clinically, they may have similar presentations. In addition, neither has a definitive diagnostic test. Our patient presented with sensorial and neurologic changes but only exhibited non-specific findings on CSF and brain imaging studies. These results could have been due to either infection or active NP-SLE disease. As is often necessary, our patient was simultaneously treated for infection and NP-SLE and the antibiotics discontinued when extensive work-up for infection did not yield any positive findings. Unfortunately, our patient had an uncommon pathogen that is difficult to diagnose. A brain biopsy may have provided a diagnosis however an *acanthamoeba* infection was not suspected.

Despite the paucity of literature on the optimal diagnostic options and treatment, successful treatment has been reported in immunocompetent hosts when the organism is identified early in the disease course (12, 13). The literature does not describe any immunocompromised patients who have had successful treatment.

When a patient with NP-SLE does not respond to conventional therapy an *acanthamoeba* infection should be considered despite negative infectious work-up. A brain biopsy may be necessary as a more timely diagnosis and treatment of this infection in the immunocompromised individual may improve its current outcome.

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