Case report

Cryptococcal meningitis; a rare cause of headache in lupus: case report and literature review

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Abstract

Microbial infections are the leading causes of morbidity and mortality in patients with Systemic Lupus Erythematosus (SLE). Cryptococcal Meningitis (CM) infection is often underestimated and misdiagnosed in patients with SLE. This partly is due to its nonspecific clinical presentations at the early stage of the disease. It commonly presents with fever and headache and has a high mortality rate in SLE patients. They are a paucity of case reports in literature worldwide. We present a case of a lupus patient who presented with confusion and in the background of chronic headache and partially treated meningitis which turned out to be cryptococcal meningitis. The case illustrates the need to have a high index of suspicion so as to initiate early treatment and avert mortality.

Key words: Systemic lupus erythematosus, Cryptococcal meningitis, Kenya

Introduction

Microbial infections are common in SLE and are the leading cause of mortality ranging from 25% to 50%[1]. At least half of all lupus patients will experience a severe infection of which more than 20% will require hospitalization during their lifetime[2]. Studies have documented risk factors for infections to be high disease activity, low complement levels, lupus nephritis, leucopenia, corticosteroid treatment at a prednisolone equivalent dose of 7.5 to 10mg/day, corticosteroid pulse therapy, and high-dose regimen of cyclophosphamide[3-5]. A Korean study noted that patients not on corticosteroid but had a high SLEDAI, anaemia, active urine sediment had an increased risk for infections[6]. The leading cause of infections is bacterial *Streptococcus pneumonia* affecting the respiratory tract, *Escherichia coli*, *Klebsiella* and *Pseudomonas spp* affecting the urinary tract and *Staphylococcus aureus* causing skin, soft tissue, bone, and joint infections[2]. In the CNS system Cryptococcal causes about 30.4–58.8% CNS infections in SLE patients[7,8]. Pathophysiology is thought to revolve around the autoimmune-mediated attack, making the CNS susceptible to infection through impairment of the blood-brain barrier[9]. There is a paucity of data on epidemiological characteristics of CM among non-HIV population including patients with SLE. Rheumatologists may underestimate the risk of CM and misdiagnose it due to its non-specific presentation, especially early in the disease, and the limited available information on the disease in lupus setting. The risk of misdiagnosis is high as alternative diagnoses to CM could be steroid-induced psychosis or lupus flare which may be difficult to differentiate, this may lead to delay in administering the right treatment[9-11]. Differentiating between lupus flare, and infection may be difficult. When patients with SLE present fevers, SLE-related manifestations, and disease activity markers indicate an SLE flare-up, and increased CRP and leukocyte count suggest a combined infection[3-6]. Majority of the cases of CM in SLE has been reported in Asia and the Americas, there is no documented case report from Africa. We report a case of CM in lupus and results of a literature review looking at presentation, treatment and outcomes.

Case report

A 33 year old lady known to have lupus presented with a 6 month history of headache. She had been diagnosed with lupus based on the SLICC criteria two and half years prior when she presented with malar rash, arthralgia, fever, and photosensitive dermatitis. She reported at diagnosis she had anaemia, low

white blood cell count, and positive ANA. Initially, she had been on mycophenolate mofetil, azathioprine, and pregabalin which she used for an unspecified duration of time. However, she reported to have been using prednisone at high doses to relieve her symptoms from time to time for the two and a half years she has had lupus. At the time of presentation, she had been on azathioprine 75 mg po once daily, hydroxychloroquine 200 mg po twice daily and prednisone 10 mg po once daily. She gave a 6-month history of headache which she described as throbbing and having affected her everyday activities. It was localized in the periorbital, vertex, and occipital regions. She had used multiple analgesics: Diclofenac, paracetamol, and tramadol with partial relief. At some point, she tried to increase the prednisolone dosage with no effect on headaches. A month after the headache started, she developed transient confusion, hallucination and fever. This was associated with a mild left-sided weakness. She was seen at a peripheral hospital and treated empirically as bacterial meningitis. Of note is that a lumbar puncture for CSF analysis was not done. Three months later, with the headaches still persistent, she was admitted at the same hospital and transfused because of a low haemoglobin level of 7. Three days before admission the headache got even more intense. She was now confused, vomiting and having photophobia. On admission, she was noted to be running a fever of 38 degrees, confused, wasted, oral ulcers typical of SLE, had thin sparse hair with temporal alopecia and skin over face and trunk was exfoliated and erythematosus. She had a full range of eye movements and no nystagmus. Visual fields were not assessable. Fundoscopy revealed normal optic discs. Other cranial nerves were intact. Her neck was stiff and kerning's sign positive. Nose and ear exams were unremarkable. She had left pyramidal weakness of 4+ at best. Bulk and reflexes were preserved and symmetrical. Plantar reflexes were mute bilaterally. Sensation, gait and cerebellar were not assessed. An impression of meningoencephalitis with differentials was partially treated bacterial meningoencephalitis, TB meningitis, a viral meningoencephalitis, neurolupus or cerebral sinus thrombosis. Her full haemogram revealed a normal white cell count of 5.23 with a neutrophil percentage of 59. She had normocytic normochromic anaemia of 8.9 mg/dl and a low platelet count of 100. CRP was slightly elevated at 11.7. Her electrolytes and kidney function were normal with a sodium of 143, creatinine of 111, sodium of 143 and potassium of 3.37. A random sugar done was at 6. 0mmol/l and her HBA1C was at 7.0%. HIV serology was negative. C3, C4, dsDNA levels were also requested. Blood cultures did not yield any growth. Lumbar puncture revealed clear CSF with an estimated pressure of 22cm of water. The analysis revealed a high protein at 1527mg/L, glucose 0.4mmo/l. Cell count of 33wbc/mm^3. There were no organisms on gram stain. India ink was negative and no growth was obtained on CSF culture. Gene expert for tuberculosis was also negative. An MRI of the brain revealed prominent leptomeningeal enhancement. There was also a small focus of gliosis in the right posterior capsuloganglionic region and chronic small vessel ischemia. MR venography ruled out cerebral thrombosis. Her EEG revealed diffuse slowing 4-6Hz Theta waves which were in keeping with diffuse cerebral dysfunction. Her chest radiograph was unremarkable.

Table 1: Showing CSF bio fire of the patient

Cytomegalovirus	Not detected
Enterovirus	Not detected
Herpes simplex 1	Not detected
Herpes simplex virus 2	Not detected
Human herpes virus 6	Not detected
Human parechiovirus	Not detected
Variecella zoster virus	Not detected
Escherichia coli	Not detected
Listeria monocytogenes	Not detected
Neiserria meningitidis	Not detected
Streptococcus agalacticae	Not detected
Streptococcus pneumonia	Not detected
Cryptococcal neoformans	Detected

The patient was started on meningitis doses of ceftriaxone. As soon as the bio fire results were out she was started on amphotericin B 50mg once a day combined with fluconazole at 1200mg daily. She was also on tramadol and paracetamol for the headache. Through the first week, the patient improved. She reported less and less headache, and her confusion completely resolved. However, she was noted to be developing some hearing loss and an ENT specialist was called to see her. Her lowest potassium was 2.4mmol/L and it was supplemented. Her urea and creatinine remained acceptable all through. On day 12, however, she was noted to be confused again. After a thorough evaluation, the thoughts were a flare of lupus with differentials of neurolupus. A decision to pulse with methylprednisolone for three days was made since we had no compliment levels for C3, C4, and dsDNA. By day two of pulsing, she was much better. The confusion had resolved and there was no headache. Her meningitis medication was continued. On day 15 she had rapid onset difficulty in breathing. The assessment revealed a tachycardia of 36, the pulse rate at 112 and blood pressure at 100/74. She was afebrile. Her chest examination revealed normal breath sounds

and her CNS examination was essentially normal. The possibility of an acute pulmonary embolism was entertained. The main differential was hospital-acquired pneumonia. She was started on clexane 80mg BD and ceftazidime as D-dimer and a pulmonary angiogram was organized. The critical care team was called to review her for possible admission to ICU but unfortunately succumbed the same evening.

Discussion

Cryptococcal Meningitis (CM) has a high prevalence rate and is often underdiagnosed due to its non-specific presentation, especially early in the disease, and the limited available information on the disease in lupus setting. There is a paucity of data on the disease and is not well understood especially outside HIV let alone in the setting of lupus. The majority of the cases of CM in SLE has been reported in Asia and the Americas, there is no documented case report from Africa. In the nervous system, cryptococcal is responsible for 30.4–58.8% CNS infections in SLE patients[7,8]. In a review by Fang *et al*[9] they reported 50.1% developed CM within a year of diagnosis of SLE with a mortality rate of 23.4%. CM is a female predominant (89.1%) disease in the setting of lupus despite the fact that outside lupus its more in males[9]. This could be because SLE has a female gender bias. Our patient was female. The overall median age has been found to be 32 years with the age younger in developing countries at 27 years[9]. Our patient was aged 33 years at the time of diagnosis. The other difference noted by Fang *et al*[9] was the role of steroids in developed and developing countries. Newly diagnosed lupus patients in developing countries were more likely to be on higher doses of steroids at the onset of the illness. This is partly due to medications being unavailable or unaffordable leading to overuse of steroids, thus, increasing the risk for treatment-related infections[9]. Higher doses of prednisolone are associated with increased infections in SLE population[5]. In the setting of CM in lupus dosing of prednisolone of ≥30 mg/day prior to infection is associated with a higher mortality rate[9]. The pathophysiology is thought to surround damage to the blood-brain barrier by the steroids causing accelerated the permeability, resulting in an increased risk of infection or worsening the clinical outcome[12]. Our patient had been on unknown high doses of prednisolone for unspecified periods which could have put her at risk for developing CM. Misdiagnosis is seen in about one in three patients with CM as the majority of the times the primary doctor didn't consider the disease at the onset[9]. Most of the time the diagnosis was made when the LP results returned as in our case. The most common alternative diagnoses include non-fungal causes of meningitis or flare of lupus[9]. This may contribute to the high mortality witnessed in CM due to the delay of the lack of initiation of the appropriate treatment. The most common presenting symptoms from the literature include headache (81.8%), fever (72.7%), vomiting (40%), neck rigidity (30.9%) and impaired consciousness (29.1%)[9]. Our patient had presented with headaches, fever and confusion. The diagnosis of CM is made on cerebral spinal fluid tests using microscopy (for example, India ink staining), culture and/or cryptococcal antigen tests after the diagnosis of LP has been made[9]. The advantage of microscopy with India ink is its rapid and inexpensive but has low sensitivity and specificity. Our patient had stained negative for India ink. Alternatively, cryptococcal antigen is available as the serum of cerebral spinal fluid is simple to carry out and have equally high sensitivity and specificity[9]. It is, therefore, recommended doing either serum or cerebral spinal fluid CRAG on lupus patients presenting with CNS symptoms[9]. Mortality from CM is high. Fang *et al*[9] reported that 33% of the deaths from CM were from refusal to take antifungal because the patient could not afford the drugs[9]. Most of the studies on CM available are in the HIV setting. CM is also seen in organ transplant and HIV negative patients. Data on the use of antifungal regimens for HIV-uninfected hosts are largely extrapolated from larger studies of patients with HIV infection[13]. Treatment is usually divided into three stages which are induction, consolidation and maintenance phases[13]. The difference between HIV positive and HIV negative is the length of the duration. In HIV negative population the induction phase can be prolonged to up to six weeks who develop neurologic complications on treatment or four weeks after the culture is negative[14]. Infectious Disease Society of America (IDSA) guidelines suggest a combination of amphotericin B deoxycholate (0.7 to 1 mg/kg IV daily) plus flucytosine (100 mg/kg/day orally in four, divided doses)[13]. However, lipid formulations of amphotericin B with flucytosine have become the favoured induction regimen for such patients in resource-available health care systems to minimize the risk of toxicity and reduce treatment interruptions, since it is critically important to complete an uninterrupted induction regimen to optimize clinical outcomes[13,14]. In the absence of flucytosine, one can substitute with fluconazole though it's inferior to the flucytosine-amphotericin combination[14]. Following induction therapy, consolidation therapy with fluconazole (400 to 800mg [6 to 12mg/kg] orally daily) should be administered for eight weeks. Consolidation therapy should then be followed by maintenance therapy with fluconazole (200 to 400mg orally daily)[13]. Maintenance azole therapy is generally tailor-made according to the patient. The recommendation is that it be given for one year after diagnosis though the duration may be warranted for those receiving very high doses of immunosuppressive agents eg, those receiving 40 mg/day of prednisone or persistently using biologic therapy. The role of steroids is controversial in the management of CM. In HIV infected patients' trials have failed to show benefits in management[16]. In lupus,

the setting is different cause control of the disease is as important as treating CM. Infections can cause a flare of lupus thus one can't just discontinue steroids. We were forced to pulse the patient after she developed what we thought was a flare of lupus unfortunately she passed on. We believe more studies are needed to advise on the role of steroids from dosing and timing of administration in such patients.

Conclusion

Because of the unfamiliarity with this infection, the nonspecific clinical presentations at the early stage of the disease, and the limited information available in the literature, rheumatologists tend to underestimate the risk of CM amongst patients living with lupus. It is commonly misdiagnosed as flare of lupus activity, steroid induced psychosis or infection from non-fungal pathogens. One should rule out CM in a patient with high disease activity, low compliment level, history of exposure to high doses of steroids who presents with headache, fever and confusion. Other risk factors may include lupus nephritis, anaemia and high-dose regimen of cyclophosphamide. Differentiating between disease flare up and infection is usually difficult but raised CRP and leucocyte count may help point towards an infection. There should be more research on prevalence studies, prophylaxis for lupus patients at risk, pathophysiology disease in lupus, faster diagnosis, treatment of the disease in lupus setting and the potential role of steroids if any in its management. This will help improve our understanding on the disease and ultimately improve outcomes of our patients.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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