

Case report

Central nervous system melioidosis in systemic lupus erythematosus: A clinical vignette



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ABSTRACT

Central nervous system melioidosis is an uncommon presentation of melioidosis infection. We report a case of a disseminated melioidosis infection with central nervous system, pulmonary, spleen, bone and cutaneous involvement in a patient with underlying systemic lupus erythematosus. The diagnosis was confirmed based on positive blood and cerebrospinal fluid cultures coupled with radiological findings. Agriculture contact and underlying immunocompromised state were the predisposing risk factors for melioidosis infection in this case. Our patient was successfully treated with 10 weeks of intensive antibiotics therapy and 1 year of eradication antibiotics therapy with significant clinical and radiological improvement.

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Introduction

Melioidosis is an endemic infectious disease in Southeast Asia and Northern Australia [1]. It has a wide spectrum of clinical presentations including severe sepsis, involvement of pulmonary, genitourinary, soft tissues and other organ systems [2]. Central nervous system (CNS) melioidosis is rare with a reported incidence of approximately one percent [2]. Fever (82%), headache (54%), unilateral weakness (57%) and cranial nerve deficits (52%) are among the common symptoms. Mortality rate can be up to 20% in delayed diagnosis [3]. We present a case of disseminated melioidosis infection with CNS, pulmonary, spleen, bone and cutaneous involvement in a female patient with underlying systemic lupus erythematosus (SLE).

Case presentation

A thirty eight years old female was diagnosed with SLE with mucocutaneous, musculoskeletal, haematological and renal involvement in April 2020. She is a dedicated kindergarten teacher who frequently involved in gardening work in the kindergarten compound for the past 15 years. The antinuclear antibody (ANA) and

double-stranded DNA antibodies were positive. The ANA showed homogenous pattern with the titre of 1:1280. She was started on hydroxychloroquine 200 mg OD and prednisolone 40 mg OD upon diagnosis of SLE. She was treated as active lupus nephritis in view of heavy proteinuria of 3.39 g/24 h. Intravenous (IV) cyclophosphamide 500 mg was then given to treat her active lupus nephritis. 1 month after her first dose of IV cyclophosphamide treatment, she presented with high grade fever and altered consciousness with Glasgow Coma Scale of 14/15. On physical examination, she had left hemiparesis with 2/5 strength in both upper and lower extremities. There was neck stiffness but all the cranial nerves function were intact. Crepitations were heard over the right lung and a few rounded erythematous subcutaneous nodules were found over the forearms which may represent septic nodules. Abdominal examination was unremarkable. She was initially treated as meningoencephalitis with IV ceftriaxone 2 g BD and IV acyclovir 500 mg TDS.

The initial laboratory tests result were as shown in Fig. 1a. Hepatitis C virus, Hepatitis B virus and human immunodeficiency virus (HIV) screening were all negative. The sputum samples were negative for tuberculosis. Plain computed tomography (CT) brain was done which showed hypodensities at the right frontal region and right parieto-occipital region which may represent infective cerebritis or lupus cerebritis. Lumbar puncture was performed with an opening pressure of 15cmH₂O and the cerebrospinal fluid (CSF) results were as shown in Fig. 1b. Her antibiotic was subsequently

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Blood test	Results	Reference range	CSF appearance	Clear
Haemoglobin level	6.7	g/dL (12.0-15.0)	Total cells	161 cells 30% polymorphonuclear cells 70% lymphocytes
Total White Cell Count	5.1	$\times 10^9/\mu\text{L}$ (4.0-10.0)	CSF protein	1.84 g/L (normal reference 0.15-0.45)
Platelet Count	260	$\times 10^9/\mu\text{L}$ (150-410)	CSF to serum glucose ratio	0.1 (low)
Urea	5.9	mmol/L (1.7-8.3)	CSF Acid-Fast Bacilli	No Acid-Fast Bacilli seen
Sodium	125	mmol/L (136-146)	Tuberculous PCR	Not detected
Potassium	4.2	mmol/L (3.5-5.1)	Indian Ink	Negative
Creatinine	85	$\mu\text{mol/L}$ (44-80)	Culture and Sensitivity	<i>B. pseudomallei</i> Sensitive to trimethoprim/sulfamethoxazole and meropenem
Albumin	20	g/L (35-52)	Tuberculous Culture and Sensitivity	No growth
Aspartate aminotransferase	55	U/L (<35)		
Alanine aminotransferase	47	U/L (<35)		
Erythrocyte sedimentation rate	104	mm/hr (<13)		
C-reactive protein	24	mg/L (<5)		

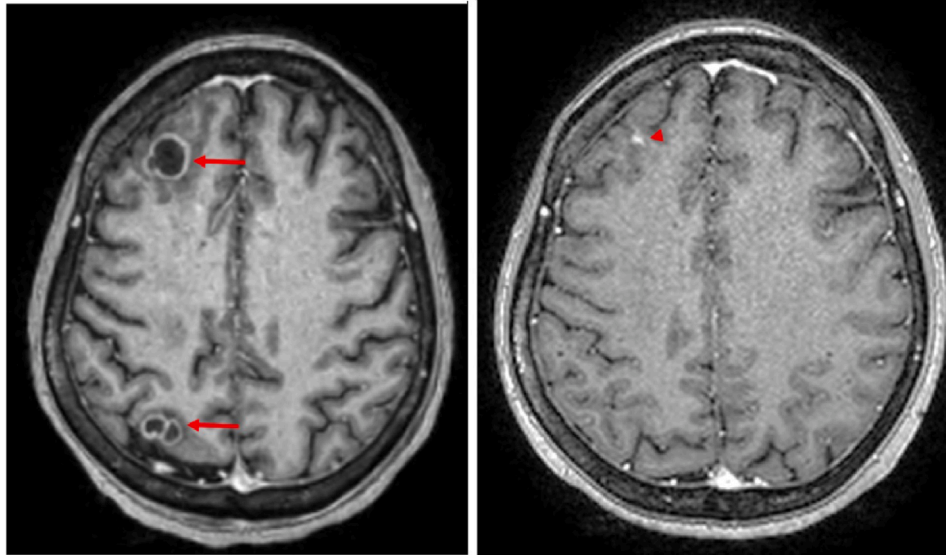


Fig. 1. (a) Initial laboratory test results. (b) CSF investigation results, CSF = Cerebrospinal Fluid, PCR = Polymerase chain reaction. (c) Baseline MRI Brain T1WI post gadolinium axial images demonstrated rim enhancing right frontal and right parietal intraaxial lesions (red arrows). (d) Post eradication therapy MRI after 20 weeks demonstrated treatment response with near resolution of lesions with a small residual right frontal lobe enhancing focus (arrowhead). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

escalated to IV meropenem 2 g TDS and IV immunoglobulin 0.4 g/kg was given for 5 days in view of worsening sepsis.

Subsequent Magnetic Resonance Imaging (MRI) of the brain revealed more than two multifocal rim-enhancing intraaxial brain lesions with the largest lesion measured at 1.5 cm \times 1.4 cm. Serial chest radiographs (CXRs) showed pulmonary nodules of varying sizes with upper lobe predominance and bilateral moderate pleural effusion. Contrast enhanced CT thorax demonstrated scattered clusters of lung nodules, mostly peripherally located, a few cavitations with air-fluid levels, suspicious of infective cavitating nodules. One liver and multiple splenic hypodense lesions were seen in the visualised upper abdomen, suspicious of microabscesses. Given the progressive imaging findings and lack of clinical improvement, anti-tuberculous agents were started empirically.

5 days later, both the blood and CSF cultures grew *Burkholderia Pseudomallei*. Her diagnosis was revised to disseminated melioidosis with CNS, pulmonary, spleen, bone and cutaneous involvement and the anti-tuberculous agents were discontinued. 2 weeks later, the full sensitivity report showed susceptible *B. Pseudomallei* towards trimethoprim/sulfamethoxazole, ceftazidime and meropenem with minimum inhibitory concentration of 2 ug/mL, 2 ug/mL and 1.5 ug/mL respectively. The antibiotics was then de-escalated to IV ceftazidime 2 g QID based on the sensitivity report. Blood cultures were repeated 1 week and 2 weeks post treatment which showed

clearance of bacteraemia. MRI brain 3 weeks post treatment demonstrated treatment response as evidenced by reduction in the size of the largest brain lesion from 1.5 cm \times 1.4 cm to 0.9 cm \times 0.8 cm. The number of intraaxial brain lesions was also reduced. However, new C2 and C3 vertebrae marrow osteomyelitis were observed. She completed 10 weeks of intensive therapy (2 weeks of IV meropenem and 8 weeks of IV ceftazidime) and was started on single strength trimethoprim/sulphamethoxazole (80 mg/400 mg) three tablets twice a day as eradication therapy. The strength of the left upper and lower extremities improved to 3/5 upon discharge.

The liver and spleen microabscesses resolved based on the repeated imaging. MRI brain and cervical was performed 20 weeks post treatment to decide on the duration of eradication therapy. MRI brain demonstrated a small residual right frontal lobe enhancing focus measuring 0.4 cm with no new cerebral lesion. MRI cervical showed improved osteomyelitis changes at C2 vertebrae. The strength of the left upper and lower extremities improved to 4/5 at this time. The eradication therapy was extended to 12 months in view of presence of cervical vertebral osteomyelitis and residual cerebral lesion. Currently, the strength of her left upper and lower extremities further improved to 5/5 and she is ambulating independently. Her SLE activity was well controlled with hydroxychloroquine 200 mg OD, azathioprine 50 mg OD and prednisolone 10 mg OD.

Discussion

Melioidosis infection is caused by *B. Pseudomallei*, a saprophytic gram negative bacillus which is commonly found in Southeast Asia and northern Australia. Modes of transmission include inhalation, direct contact with infected food, soil, water, excreta or inoculation from contaminated soil. The risks of infection is higher among those with high risks occupation with exposure to the contaminated soil and water. According to one local study in Malaysia, the proportion of cases is significantly greater among people involved in forestry, farming and fishing [4]. Paul Vijay Kingsley et.al conducted a computerised review of case reports of melioidosis in Malaysia from 1975 to 2015. A total of 67 cases were reported and 5 (7.5%) were found to have primary neurological manifestation [5]. Diabetes mellitus remained as one of the most important risk factors for melioidosis. SLE could also be one of the risk factors for melioidosis infection. A young girl with underlying SLE was reported by Prayong Vachvanichsanong et.al to have melioidosis with cerebral abscess [6]. Our patient was empirically treated as active lupus nephritis in view of heavy proteinuria. She was planned for six cycles of monthly IV cyclophosphamide based on the National Institute of Health (NIH) guideline. Unfortunately, she had melioidosis infection 1 month after her first dose of IV cyclophosphamide. *B. pseudomallei* infection can remain latent for a long period of time after the initial exposure and cause clinically significant infection when the host immune system is suppressed. Wells et.al reported a case of melioidosis septic arthritis which presented 36 years post exposure [7]. Our patient could have exposed to the contaminated soil for the past 15 years in conjunction with her gardening work. The bacteria likely remained latent in her body and clinically manifested post immunosuppressants for her newly diagnosed SLE.

Imaging demonstrated disseminated pulmonary and extra-pulmonary (CNS, spinal, visceral) infective seeding in this case. However, distinguishing melioidosis and tuberculosis based on imaging alone is difficult due to non-specific overlapping radiological signs. Harvey J et.al described findings of cerebral abscesses, isolated encephalitis, and leptomeningeal enhancement in melioidosis which is seen in our case [8]. In the lungs, preferential upper lobe pulmonary involvement and multiple cavitating nodules may be present in both disease pathologies. Confluent consolidations which coalesce before thin wall cavity formation are more often seen in *Bukholderia* [9]. Co-infections with melioidosis and pulmonary tuberculosis have also been reported in patients with diabetes mellitus [10]. Hence, cultures or tissue diagnoses are of paramount importance in confirming the exact causative organism for disseminated infection. According to a systemic review of CNS melioidosis in 2019, 41% has positive blood cultures and 19% has positive CSF cultures out of 110 patients with CNS melioidosis [3].

Melioidosis therapy is divided into an intravenous intensive phase and an oral eradication phase. According to the 2010 census recommendation, IV ceftazidime and IV meropenem are recommended for intensive-phase therapy, while trimethoprim/sulfamethoxazole is the first-line drug for eradication-phase therapy [11]. According to the 2020 Review and revision of the 2015 Darwin melioidosis treatment guideline, the recommended minimum intensive-phase therapy and eradication-phase therapy for CNS melioidosis are 8 weeks and 6 months respectively [12]. The cause of recrudescence and relapse is usually due to unidentified osteomyelitis and deep-seated abscess. In our case, the intensive-phase therapy was extended to 10 weeks and eradication-phase therapy was extended to 12 months in view of presence of cervical vertebrae osteomyelitis and residual cerebral lesion on repeated scan at 20 weeks of eradication therapy.

Conclusion

Our case highlighted the challenges faced in managing a SLE patient with disseminated melioidosis infection post cyclophosphamide treatment. High clinical suspicion in immunocompromised patients with epidemiological exposure is the key for prompt empirical treatment prior to the confirmatory culture results.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Consent

This article does contain studies with human participant and was registered via National Medical Research Register Malaysia with a Research ID of NMRR-20-1721-55996.

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Credit authorship contribution statement

LHC was responsible for the study design, data collection, and manuscript writing. ASOT, SD, YLW, YKC, SCN and WMC participated in data collection and contributed to case illustration and discussion. HHC and CLT were involved in the manuscript editing and language proofreading. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest and financial disclosure.

References

- [1] Deuble M, Aquilina C, Norton R. Neurologic melioidosis. *Am J Trop Med Hyg* 2013;89(3):535–9.
- [2] Madi D, Rai SPV, Vidyalakshmi K, Chowta KN. Neurological melioidosis presenting as intracranial abscess. *Indian J Pathol Microbiol* 2016;59(3):417–9.
- [3] Wongwandee M, Linasmita P. Central nervous system melioidosis: a systematic review of individual participant data of case reports and case series. *PLoS Negl Trop Dis* 2019;13(4):0007320.
- [4] Hassan MR, Pani SP, Peng NP, Voralu K, Vijayalakshmi N, Mehanderkar R, Aziz NA, Michael E. Incidence, risk factors and clinical epidemiology of melioidosis: a complex socio-ecological emerging infectious disease in the Alor Setar region of Kedah, Malaysia. *BMC Infect Dis* 2010;10:302.
- [5] Kingsley PV, Leader M, Nagodawithana NS, Tipre M, Sathiakumar N. Melioidosis in Malaysia: a review of case reports. *PLoS Negl Trop Dis* 2016;10(12):0005182.
- [6] Vachvanichsanong P, Dissaneewate P, Prukprasert P, Wongchanchailert M, Thongmak S, Janjindamai S, et al. Melioidosis and brain abscess in a girl with systemic lupus erythematosus. *Infect Dis Clin Pract* 2002;11(4):211–3.
- [7] Wells EV, Cinti SK, Clark TA, Rudrik JT, Boulton ML. Melioidosis-reactivation of latent disease: case presentation and review. *Infect Dis Clin Pract* 2011;19(3):161–6.
- [8] Harvey J, Boles B, Brown D. A review of imaging findings in melioidosis: revealing the tropics' dirty secret. *Int J Infect Dis* 2020;7(4):176–85.

- [9] Mukhopadhyay C, Krishna S, Vandana Ke, Saravu K, Balasubramaniam R. Tuberculosis or melioidosis? - Look twice in south-western coastal India. SAARC J Tuberc Lung Dis HIV/AIDS 2012;IX(2):15–8.
- [10] Shetty AK, Boloor R, Sharma V, Bhat GHK. Melioidosis and pulmonary tuberculosis co-infection in a diabetic. Ann Thorac Med 2020;5(2):113–5.
- [11] Lipsitz R, Garges S, Aurigemma R, Baccam P, Blaney DD, Cheng AC, Currie BJ, Dance D, Gee JE, Larsen J, Limmathurotsakul D, Morrow MG, Norton R, O'Mara E, Peacock SJ, Pesik N, Rogers LP, Schweizer HP, Steinmetz I, Tan G, Tan P, Wiersinga WJ, Wuthiekanun V, Smith TL. Workshop on treatment of and postexposure prophylaxis for Burkholderia pseudomallei and B. mallei infection. 2010. Emerg Infect Dis 2012;18:2.
- [12] Sullivan RP, Marshal CS, Anstey NM, Ward L, Currie BJ. 2020 Review and revision of the 2015 Darwin melioidosis treatment guideline; paradigm drift not shift. PLoS Negl Trop Dis 2020;14(9):e0008659.